Dr. Adnan Aydiner
Dr. Ahmet Kızır
Dr. Vahit Ozmen
Dr. Merdan Fayda

Summary of St Gallen consensus 2013
Istanbul University Institute of Oncology, 29 Mart 2013
Geographical and professional composition of the consensus panel at St Gallen 2013

A total of 48 breast cancer experts (including 2 chairmen) from 21 countries worldwide

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>25</td>
</tr>
<tr>
<td>USA, Canada and South America (Peru)</td>
<td>17</td>
</tr>
<tr>
<td>Austal-Asia (Australia, China and Japan)</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Professional composition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical oncology</td>
<td>27</td>
</tr>
<tr>
<td>Surgery, gynaecology</td>
<td>13</td>
</tr>
<tr>
<td>Pathology, basic research</td>
<td>4</td>
</tr>
<tr>
<td>Radio-oncology</td>
<td>2</td>
</tr>
<tr>
<td>Statistics, epidemiology</td>
<td>2</td>
</tr>
<tr>
<td>Conference Topics</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Adjuvant systemic therapy</td>
<td></td>
</tr>
<tr>
<td>Follow up</td>
<td></td>
</tr>
</tbody>
</table>
Conference Topic

Surgery
When considering breast conserving surgery which factors are contraindication?
Selection Criteria for BCT

**Biological**
- Histology
- Grade
- Nodal status
- ER
- HER2

**Mechanical**
- Extent of disease in breast
  - Negative margins
  - Diffuse calcifications
  - Multicentricity
- Ability to give RT
  - Prior RT
  - Active SLE, scleroderma
DFS and OS by Subtype

A 5 tumor subtypes (based upon Fig 1)

B 5 tumor subtypes (based upon Fig 1)

Morrow M, 13th St. Gallen IBCC, 2013

# Characteristics By Subtype

n=6072

<table>
<thead>
<tr>
<th></th>
<th>ER/PR+ HER2-</th>
<th>ER/PR+ HER2+</th>
<th>ER- HER2+</th>
<th>ER/PR- HER2-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%High Grade</td>
<td>29</td>
<td>62</td>
<td>88</td>
<td>85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>%Multifocal/centric</td>
<td>27</td>
<td>30</td>
<td>37</td>
<td>22</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>%EIC</td>
<td>15</td>
<td>25</td>
<td>27</td>
<td>9</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
### Molecular Subtype and LR After BCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
<th>n</th>
<th>%LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lum A</td>
</tr>
<tr>
<td>Millar</td>
<td>5 yr</td>
<td>498</td>
<td>1.0</td>
</tr>
<tr>
<td>Voduc</td>
<td>10</td>
<td>1461</td>
<td>8</td>
</tr>
<tr>
<td>Arvold</td>
<td>5yr</td>
<td>1434</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* No adjuvant transtuzumab

Morrow M, 13th St. Gallen IBCC, 2013
# Molecular Subtype and LR After Mastectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
<th>n</th>
<th>%LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyndi</td>
<td>5 yr</td>
<td>498</td>
<td>Lum A: 2</td>
</tr>
<tr>
<td>Voduc</td>
<td>10</td>
<td>2985</td>
<td>Lum A: 8</td>
</tr>
</tbody>
</table>

* No adjuvant transtuzumab
Effect of Transtuzumab on LRR in HER2+ Patients

Memorial Sloan-Kettering Cancer Center

T1-T2 N0, HER2+ BCS + RT

Dx 2002-2008

No transtuzumab
N=70, 3 yr LRR: 7%
Dx 2002-2004

Transtuzumab
N=102, 3 yr LRR: 1%
Dx 2005-2008

p=0.01

Morrow M, 13th St. Gallen IBCC, 2013
Is there evidence in the higher-risk triple negative subset that bigger surgery is better surgery?

LRR in triple negative Breast Cancer T1, T2 N0

<table>
<thead>
<tr>
<th></th>
<th>BCT (n=223)</th>
<th>MRM, No RT (n=235)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr LRR free survival</td>
<td>96%</td>
<td>90%</td>
<td>0.022</td>
</tr>
</tbody>
</table>

- **Multivariate HR: MRM vs BCT**
  - 2.52, 95% CI 1.11-5.72; p=.027
  - 2.53, 95% CI 1.12-5.75; p=.026
The proven risk factors for LR after BCT (HR>2)

- Gross incomplete resection (invasive and DCIS): everybody knows
- No radiotherapy
- Young age (<35 yrs)
- Biology: BRCA1/2, gene signature?
Conclusions

- Locoregional outcomes vary by molecular subtype.
- Bigger surgery does not overcome bad biology.
- Effective systemic therapy decreases LR.
- Increasingly effective multimodality therapy offers
- The chance to decrease surgical morbidity.
Who should not have BCT?
To conclude for coming Monday:

Family history of BC:
• No

BRCA1/2 mutation carrier:
• Not in itself, risk must be discussed

Involved margins:
• YES, after maximal/optimal attempt to achieve clear margins
Who should not have BCT?
To conclude for coming Monday:

No possibility for adequate radiotherapy:
• YES

Unfavorable biology on gene expression profiling:
• ?, needs further research

Patient prefers mastectomy:
• YES, provided patient is informed well in a neutral way
When considering breast conserving surgery which of the following factors are basic contraindication?

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Young Age &lt;35; &lt;40</td>
</tr>
<tr>
<td>2</td>
<td>Extensive or diffuse microcalcifications</td>
</tr>
<tr>
<td>3</td>
<td>Multifocal disease</td>
</tr>
<tr>
<td>4</td>
<td>Multicentric disease</td>
</tr>
<tr>
<td>5</td>
<td>Tumor close to nipple</td>
</tr>
<tr>
<td>7</td>
<td>Extensive vascularization</td>
</tr>
<tr>
<td>8</td>
<td>Extensive intraductal component</td>
</tr>
<tr>
<td>9</td>
<td>Lobular histology</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery, the following factor is contraindication.

**Important:** In the following questions, answering Yes in "Absolute" meant that the panelist had to abstain in the subsequent question on "Relative".

**For abstain:** Panelists were advised to abstain if they felt that the issue had insufficient data, or if the panelist did not consider themselves an expert in that particular issue, or if there was a potential conflict of interest.
When considering breast conserving surgery the following factor is contraindication

Age < 35

- Absolute: Yes 89.6%, No 4.1%, Abstain 6.3%
- Relative: Yes 60.9%, No 8.7%

Age < 40

- Absolute: Yes 93.5%, No 2.2%, Abstain 4.3%
- Relative: Yes 88.6%
When considering breast conserving surgery the following factor is contraindication:

### Extensive or diffuse microcalcifications

<table>
<thead>
<tr>
<th>Factor</th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive or diffuse microcalcifications</td>
<td>Yes: 19.1</td>
<td>No: 6.4</td>
</tr>
<tr>
<td></td>
<td>74.5</td>
<td>69.6</td>
</tr>
</tbody>
</table>

13th St. Gallen IBCC, 2013
When considering breast conserving surgery the following factor is contraindication:

**Multifocal Disease**

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>6.7</td>
<td>42.6</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>88.9</td>
<td>53.2</td>
</tr>
<tr>
<td><strong>Abstain</strong></td>
<td>4.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following factor is contraindication

Multicentric Disease

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>30.4</td>
<td>65.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Relative</td>
<td>76.9</td>
<td>15.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following factor is contraindication:

Tumor close to nipple

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>95.9</td>
<td>53.2</td>
</tr>
<tr>
<td>No</td>
<td>4.1</td>
<td>42.6</td>
</tr>
<tr>
<td>Abstain</td>
<td>0</td>
<td>4.3</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following factor is contraindication:

**Extensive vascular invasion**

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6.5</td>
<td>69</td>
</tr>
<tr>
<td>No</td>
<td>91.3</td>
<td>26.2</td>
</tr>
<tr>
<td>Abstain</td>
<td>2.2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

A. Aydiner
When considering breast conserving surgery the following factor is contraindication

Extensive intraductal component

<table>
<thead>
<tr>
<th>Factor</th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive intraductal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Extensive intraductal</td>
<td>2,1</td>
<td>34,7</td>
</tr>
<tr>
<td>Extensive intraductal</td>
<td>95,7</td>
<td></td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following factor is contraindication:

**Lobular histology**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute</strong></td>
<td>4.8</td>
<td>92.9</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Relative</strong></td>
<td>6.7</td>
<td>91.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

A. Aydiner
When considering breast conserving surgery the following basic factors **ARE NOT ABSOLUTE contraindications.**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Young Age &lt;35; &lt;40</td>
</tr>
<tr>
<td>2</td>
<td>Extensive or diffuse microcalcifications</td>
</tr>
<tr>
<td>3</td>
<td>Multifocal disease</td>
</tr>
<tr>
<td>4</td>
<td>Multicentric disease</td>
</tr>
<tr>
<td>5</td>
<td>Tumor close to nipple</td>
</tr>
<tr>
<td>7</td>
<td>Extensive vascularization</td>
</tr>
<tr>
<td>8</td>
<td>Extensive intraductal component</td>
</tr>
<tr>
<td>9</td>
<td>Lobular histology</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following basic factors are RELATIVE contraindications.

1. Extensive or diffuse microcalcifications
2. Multicentric disease
3. 
4. 
5. 
6. 
7. 
8. 
9. 
When considering breast conserving surgery which of the following factors are relative contraindications?

<table>
<thead>
<tr>
<th></th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Family history</td>
</tr>
<tr>
<td>2</td>
<td>BRCA1 positivity</td>
</tr>
<tr>
<td>3</td>
<td>BRCA2 positivity</td>
</tr>
<tr>
<td>4</td>
<td>Involved margins after repeated excisions (including DCIS)</td>
</tr>
<tr>
<td>5</td>
<td>Unfavourable biology on gene expressing/sequencing</td>
</tr>
<tr>
<td>6</td>
<td>Contraindications to breast irradiation that should follow breast conserving therapy</td>
</tr>
</tbody>
</table>
When considering breast conserving surgery the following factor is **relative contraindication**.

<table>
<thead>
<tr>
<th></th>
<th>Family history</th>
<th>BRCA1 Positivity</th>
<th>BRCA2 Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>0</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Yes</td>
<td>95.9</td>
<td>54.3</td>
<td>51.1</td>
</tr>
<tr>
<td>No</td>
<td>4.1</td>
<td>43.5</td>
<td>46.8</td>
</tr>
<tr>
<td>Abstain</td>
<td>4.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Legend: Yes, No, Abstain
When considering breast conserving surgery the following factor is **relative contraindication**.

Involved margins after repeated excision (including DCIS)

- **Yes**: 95.9%
- **No**: 2
- **Abstain**: 2

A. Aydiner
When considering breast conserving surgery the following factor is relative contraindication.

Unfavourable biology on gene expressing/sequencing

- Yes: 93.8%
- No: 6.3%
- Abstain: 0%
When considering breast conserving surgery the following factor is **relative contraindication**.

Contraindications to breast irradiation that should follow breast conserving therapy

- Yes: 93.8%
- No: 4.2%
- Abstain: 2.1%
When considering breast conserving surgery the following factors are relative contraindications.

1. BRCA1 positivity
2. BRCA2 positivity
3. Involved margins after repeated excisions (including DCIS)
4. Contraindications to breast irradiation that should follow breast conserving therapy

A. Aydiner
Comments

Michael Gnant said that he was very happy about this vote because the panel did not identify a single absolute contraindication for breast conservation. He was also happy that, for the first time, we have moved away from a formulistic definition of who needs to have mastectomy.
Surgery of the primary breast cancer

Is skin nipple sparing mastectomy an acceptable treatment without RT?

- Yes: 66.7%
- No: 21.4%
- Abstain: 11.9%

A. Aydiner

13th St. Gallen IBCC, 2013
Surgery of the primary breast cancer

Is skin nipple sparing mastectomy an acceptable treatment if only margin toward nipple is tumor free and immediate reconstruction planned?

- Yes: 55.3%
- No: 15.8%
- Abstain: 28.9%
Surgery of the primary breast cancer

Should MRI be routine for patients with newly diagnosed disease (to assess decision on BCS)?

- Yes: 89.8%
- No: 10.2%
- Abstain: 0%

A. Aydiner
In woman undergoing breast conserving surgery what is the minimum appropriate surgical margin?
The proven risk factors for LR

Local Recurrence by Margin Status in Breast Conserving Therapy

- Negative Margin 5%
- Close Margin 7%
- Positive Margin 12%

P = 0.03

Rutgerz E, 13th St. Gallen IBCC, 2013
Risk factors: no RT

Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year recurrence and 15-year breast cancer death: 10 801 women in 17 trials

Rutgerz E, 13th St. Gallen IBCC, 2013

EBCTCG, Lancet 2011; 378: 1707–16
TWO POSITIVE MARGIN EXCISIONS

SPECIMEN IN OR

SPECIMEN IN PATHOLOGY

4 MM MARGIN

<1 MM MARGIN
What is a negative margin?

- No ink on tumor?
- 1 mm?
- > 1 mm?
- >2 mm?
- >5 mm?

Close margin
"Close Margins" v.s. Wider Margins

- Park Joint Center 2000 No difference
- Singletary 34 studies 2002 No difference
- Houssami 21 studies 2010 No difference
Excision Goal: Avoid Positive Margins

- Relate margin width to size of tumor
- Neo-adjuvant chemo- or hormonal therapy >
- Careful margin evaluation in OR
- Thouch prep or frozen section before closing
- Shave biopsy of cavity margins
- Intra-operative ultrasound guidance
- Electromagnetic margin probes
## In-op Ultrasound Guidance

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Positive margin rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpation guided surgery</td>
<td>16.4 %</td>
</tr>
<tr>
<td>U/S guided surgery</td>
<td>3.3 %</td>
</tr>
</tbody>
</table>

Electro-magnetic Margin Probe
INVESTIGATIONAL
Particular Risk Groups
(not including BRCA Mutation Patients)

- Younger patients: <50, <40, <35 yrs
- “Triple negative” biology, basal profile
- Extensive DCIS in specimen
- Multifocal or multicentric primary
- Larger tumors
- Spotty response to neoadjuvant therapy
Conclusions

- Diagnose by core biopsy before attempting excision.
- Integrate: tumor size and biology, patient age, multifocality, breast size, location of tumor in breast -- goal is clear margins in a normal looking breast.
- Positive margins are being under-treated, RE-EXCISE.
- Negative margins are being over-treated, IF NO INK ON TUMOR SURFACE, NEED NOT RE-EXCISE.
Surgery of the primary breast cancer

In woman undergoing breast conserving surgery the minimum appropriate surgical margin is:

**Important**: In the following, if the panelist responded Yes then they had to Abstain the remaining questions...
### Surgery of the primary breast cancer

In woman undergoing breast conserving surgery the minimum appropriate surgical margin is

<table>
<thead>
<tr>
<th>Margin</th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ink on invasive tumor</td>
<td>72.9</td>
<td>20.8</td>
<td>6.3</td>
</tr>
<tr>
<td>1 mm clearence (invasive)</td>
<td>48.1</td>
<td>25.9</td>
<td>25.9</td>
</tr>
<tr>
<td>3 mm clearence (invasive)</td>
<td>61.5</td>
<td>30.8</td>
<td>7.7</td>
</tr>
<tr>
<td>5 mm clearence (invasive)</td>
<td>86</td>
<td>4.7</td>
<td>9.3</td>
</tr>
<tr>
<td>Dependent on tumor biology</td>
<td>77.6</td>
<td>18.4</td>
<td>4.1</td>
</tr>
</tbody>
</table>

- Yes
- No
- Abstain

A. Aydiner
Surgery of the primary breast cancer

Should the criteria that you have just identified be any different if there is DCIS at the margin (in a woman with invasive breast cancer)?

- Yes: 41.5%
- No: 53.7%
- Abstain: 4.9%
Comments

- **William Wood** stated that if there is DCIS at the ink then that is a positive margin still.

- **Monica Morrow** said that the vote in which 73% of respondents stated that the tumour is not on ink suggests that if you are taking out small specimens then there is not much role for things like oncoplastic surgery; this also minimizes excision and overall these factors are very positive for patients.
Surgery of the primary breast cancer

- Skin nipple sparing mastectomy is an acceptable treatment without RT.

- Skin nipple sparing mastectomy is an acceptable treatment in only if margin toward nipple is tumor free and immediate reconstruction planned.

- MRI should not be routine for patients with newly diagnosed disease (to assess decision on breast conserving surgery).

- In woman undergoing breast conserving surgery the minimum appropriate surgical margin is: “no ink on invasive tumor”.
In patients with macrometastasis in 1-2 sentinel lymph nodes, when completion of axillary dissection can safely be omitted?
Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23–01 investigators
IBCSG 23-01
Apr 2001 – Feb 2010

T ≤ 5 cm cN0
BCS or MASTECTOMY

SNB

MICROMETASTASES
931 Pts

R

FOLLOW UP
467 pts

AXILLARY
DISSECTION
464 pts
<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>AD (n=464)</th>
<th>No AD (n=467)</th>
<th>Total (n=931)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>44 (9%)</td>
<td>42 (9%)</td>
<td>86 (9%)</td>
</tr>
<tr>
<td>BCS</td>
<td>420 (91%)</td>
<td>425 (91%)</td>
<td>845 (91%)</td>
</tr>
<tr>
<td><strong>RT on BCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>10 (2%)</td>
<td>12 (3%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Intraoperative only</td>
<td>79 (19%)</td>
<td>80 (19%)</td>
<td>159 (19%)</td>
</tr>
<tr>
<td>Postoperative only</td>
<td>293 (70%)</td>
<td>297 (70%)</td>
<td>590 (70%)</td>
</tr>
<tr>
<td>Combination RT</td>
<td>36 (9%)</td>
<td>35 (8%)</td>
<td>71 (8%)</td>
</tr>
<tr>
<td>Unspecified RT</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any systemic therapy</td>
<td>441 (95%)</td>
<td>451 (97%)</td>
<td>892 (96%)</td>
</tr>
<tr>
<td>Hormonal therapy only</td>
<td>292 (63%)</td>
<td>315 (67%)</td>
<td>607 (65%)</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>42 (9%)</td>
<td>33 (7%)</td>
<td>75 (8%)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>107 (23%)</td>
<td>103 (22%)</td>
<td>210 (23%)</td>
</tr>
</tbody>
</table>
Disease-Free Survival

Galimberti, V et al. The Lancet Oncology March 2013
Overall Survival

Galimberti, V et al. The Lancet Oncology March 2013
**IBCSG 23-01 trial**

- “Not giving AD to patients with 1 or more SN micrometastases has no adverse influence on DFS or OS”

- This is level 1 evidence in favour of the St Gallen 2011 recommendation that axillary dissection should not be performed if the sentinel node contains only micrometa
Trial Z0011
(closed 12/04 at n=891)
OS and DFS in trial Z0011
Survival of the ALND Group compared with SLND-Alone Group

5-yrs OS:
AD  91.8% (89.1-94.5)
No AD  92.5% (90.0-95.1)

5-yrs DFS:
AD  82.2% (78.3-86.3)
No AD  83.9% (80.2-87.9)

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Giuliano AE et al. JAMA. 2011;305(6):569-575
Z0011 Conclusion

“it is time to abandon AD in early BC pts with a positive SN provided they receive systemic adjuvant treatment and whole breast RT”
## Criticisms of Z0011

<table>
<thead>
<tr>
<th>Criticisms</th>
<th>Rebuttals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial closed recruiting only half projected number of pts</td>
<td>No difference in 5-yr OS</td>
</tr>
<tr>
<td>Might not have power to detect a small difference in outcomes between groups</td>
<td>No difference in 5-yr DFS</td>
</tr>
<tr>
<td>Axillary recurrence rate in the no AD arm double that in the AD arm</td>
<td>Excellent OS and DFS in no AD group</td>
</tr>
<tr>
<td>Non-inferiority criterion too lax (5 yr survival in the no AD arm assumed not less than 75% of that in the AD arm)</td>
<td>In fact OS and DFS non significantly better in no AD arm</td>
</tr>
<tr>
<td>No AD = no information on any additional axillary involvement that may change adjuvant treatment</td>
<td>Low rate of axillary disease in no AD arm</td>
</tr>
<tr>
<td></td>
<td>Data indicate that complete axillary information almost never changes adjuvant treatment</td>
</tr>
</tbody>
</table>
Take Home Massage

- For most patients with early breast cancer and a clinically negative axilla, a positive SN should not be further treated.
- Caution: the decision should continue to consider all the relevant factors including patient age, comorbidities, and also patient preference.
Surgery of the axilla

In patients with macrometastasis in 1-2 sentinel lymph nodes, completion of axillary dissection can safely be omitted following:

- Mastectomy (no RT planned)
- Mastectomy (RT planned)
- Conservative resection and RT

[Bar chart showing percentages]
Surgery of the axilla

In patients otherwise undergoing breast conserving surgery, completion of axillary dissection is necessary if:

- Clinical N1: 87.5% Yes, 8.3% No, 4.2% Abstain
- Nodal status (e.g. N4+) needed for chemotherapy choice: 59.1% Yes, 38.6% No, 2.3% Abstain
Comments

Monica Morrow stated that it is very encouraging to see much greater acceptance of lack of dissection for one or two macrometastases in patients having breast conservation where the data actually exist. To address another point on young women with ER- tumours, she said that she was unable to find any data that says age is a predictor of nodal failure; ER negativity is actually associated with a lower nodal disease burden. We also need to be careful about extrapolating the data beyond what we know is safe and we really have no data addressing any of the circumstance of clinical positive nodes or three or more nodes that are associated with heavy disease burdens. Furthermore, however many sentinel nodes either turn blue or hot is how many need to be removed; the eligibility criteria in study Z11 does absolutely not mean you need to remove three nodes every time. What is important is that you stick your hands in there and feel to make sure you are not leaving behind gross nodal disease, bearing in mind that a lot of patients have only one sentinel node.
Surgery of the axilla

- In patients with macrometastasis in 1-2 sentinel lymph nodes, completion of axillary dissection can safely be omitted following BCT and RT.

- In patients otherwise undergoing breast conserving surgery, completion of axillary dissection is necessary if:
  - There is clinical N1 disease,
  - If nodal status needed for chemotherapy choice.
Conference Topic

Radiation therapy
Is there a group not requiring radiotherapy as part of Breast Conserving Therapy (BCT)?
**Radiotherapy: Conserved Breast Irradiation**

- >70 y Stage I, ER+, if able to take TMX, RT may be omitted
  - TAM vs. Tam+RT
  - FU: 10.5 years

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>Tam+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional recurrence</td>
<td>%9</td>
<td>%2</td>
</tr>
<tr>
<td>10y Mastectomy free survival</td>
<td>%96</td>
<td>%98</td>
</tr>
<tr>
<td>10 yr DMFS</td>
<td>%95</td>
<td>%93</td>
</tr>
</tbody>
</table>

DMFS: Distant metastatic free survival

Hughes, ASCO 2010
Radiotherapy: Conserved Breast Irradiation

Is there a group not requiring RT as part of BCT?

- Yes: 68.2%
- No: 27.3%
- Abstain: 4.2%
Should short course RT (e.g. 40 Gy in 15 fractions) be offered as standard?
# Hypofraction RT Trials

<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>Start A UK *</th>
<th>Start B UK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of pts</strong></td>
<td>1234</td>
<td>2236</td>
<td>2215</td>
</tr>
<tr>
<td><strong>Med. Follow up</strong></td>
<td>12 yr</td>
<td>9,3 yr</td>
<td>9,9 yr</td>
</tr>
<tr>
<td><strong>Arms (Gy x fr number)</strong></td>
<td>2x25/5 wk, 2,66x16/3 wk</td>
<td>2x25/5 wk, 3x13/5 wk, 3,2x13/5 wk</td>
<td>2x25/5 wk, 2,66x15/3 wk</td>
</tr>
</tbody>
</table>

*Trial to determine α/β ratio

Harris, SGBCC, 2013
Radiotherapy: Conserved Breast Irradiation

No. at Risk
Standard regimen 612 606 594 583 573 559 535 519 505 487 453 355 242
Hypofractionated regimen 622 617 605 592 576 562 539 517 495 482 455 369 241

Whelan, NEJM, 2010
Radiation Therapy: Conserved Breast Irradiation

**Trial B: Results**

<table>
<thead>
<tr>
<th>% free of adverse effects</th>
<th>Rate of local-regional tumor relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>90</td>
<td>0.09</td>
</tr>
<tr>
<td>80</td>
<td>0.08</td>
</tr>
<tr>
<td>70</td>
<td>0.07</td>
</tr>
<tr>
<td>60</td>
<td>0.06</td>
</tr>
<tr>
<td>50</td>
<td>0.05</td>
</tr>
<tr>
<td>40</td>
<td>0.04</td>
</tr>
<tr>
<td>30</td>
<td>0.03</td>
</tr>
<tr>
<td>20</td>
<td>0.02</td>
</tr>
<tr>
<td>10</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Hazard Ratio (95% CI)**

- 40 Gy vs. 50 Gy: 0.77 (0.66-0.89)
- 40 Gy vs. 50 Gy: 0.77 (0.51 – 1.16)

Yarnold, SABC 2012
# Radiotherapy: Conserved Breast Irradiation

<table>
<thead>
<tr>
<th></th>
<th>Canada, %</th>
<th>START B, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER –</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Grade 3</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Age &lt; 50</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Boost</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>Nodal RT</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Chemo</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Harris, SGBCC, 2013
Radiotherapy: Conserved Breast Irradiation

<table>
<thead>
<tr>
<th>ASTRO 2011 Hipofx Breast RT Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Stage</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Fractionation</td>
</tr>
<tr>
<td>Heart in field</td>
</tr>
<tr>
<td>Boost</td>
</tr>
<tr>
<td>Dose Homogeneity</td>
</tr>
</tbody>
</table>

Smith, IJROBP, 2011
## Radiotherapy: Conserved Breast Irradiation

### New DFCI / BWH Approach

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Stage</td>
<td>$\geq 50$ y, DCIS $\geq 60$, Tangents only</td>
</tr>
<tr>
<td>Surgery</td>
<td>Breast conserving surgery</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>OK</td>
</tr>
<tr>
<td>Fractionation</td>
<td>$2.66 \text{ Gy } \times 16$</td>
</tr>
<tr>
<td>Heart in feld</td>
<td>0</td>
</tr>
<tr>
<td>Boost</td>
<td>$2.5 \text{ Gy } \times 2-4$</td>
</tr>
<tr>
<td>DoseHomogeneity</td>
<td>$\leq 7%$</td>
</tr>
</tbody>
</table>

References:
- Harris, SGBCC, 2013
Radiotherapy: Conserved Breast Irradiation

Should “short course” RT (e.g. 40 Gy in 15 fractions) be offered

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>as standard</td>
<td>59.2</td>
<td>30.6</td>
<td>10.2</td>
</tr>
<tr>
<td>as standard in some patients</td>
<td>72.2</td>
<td>11.1</td>
<td>16.7</td>
</tr>
<tr>
<td>as an option if boost is also planned</td>
<td>77.8</td>
<td>4.4</td>
<td>17.8</td>
</tr>
</tbody>
</table>
**Comments**

- **Jay Harris** stated that, with regard to the first point, it is very clear that in patients who are younger, radiation after breast conserving surgery improves long-term survival but as patients age the survival advantage decreases due to competing risks and so the answer to the first question is clearly yes, mostly predicated on age and comorbidities. We’ve just seen such good data for short course radiotherapy and it is likely that over time more of us will say this is standard therapy but in the US we are still not quite there.

- **Felix Sedmayer** added that while this may be common practice in the US this is quite the opposite of the situation in Europe, as reflected by most European guidelines. Not a single cohort has been identified up until now where radiotherapy can be omitted safely without compromising local tumour control. These patients with low risk are the focus of reduced radiotherapy.
Following breast conserving surgery Partial Breast Irradiation (PBI) may be used as the definitive irradiation without any external beam therapy (ASTRO/ESTRO group)?
## PBI Clinical Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Med. FU</th>
<th>Local Relaps %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budapest</td>
<td>120 months</td>
<td>5,5 %</td>
</tr>
<tr>
<td>[HDR 5,2 Gy x 7 fr / 4 days or 50 Gy é]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targit</td>
<td>29 months</td>
<td>3,3 %</td>
</tr>
<tr>
<td>[50KeV, 20 Gy at surface of the applicator 5-7Gy at 1cm]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIOT</td>
<td>63 months</td>
<td>5,3 %</td>
</tr>
<tr>
<td>[electron, 21 Gy to %90 isodose line]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIOT out trial</td>
<td>60 months</td>
<td>6 %</td>
</tr>
<tr>
<td>Mamosite Registry</td>
<td>42 months</td>
<td>3,8 %</td>
</tr>
<tr>
<td>[3,4 Gy to 1 cm x 10 fr ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Orecchia, SGBCC, 2013
### 5-y Local Relapse Rates after BCS+WBI

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06</td>
<td>(1976-1984)</td>
<td>14.3</td>
</tr>
<tr>
<td>CRC, UK</td>
<td>(1981-1990)</td>
<td>19.7</td>
</tr>
<tr>
<td>Ontario COG</td>
<td>(1984-1989)</td>
<td>11</td>
</tr>
<tr>
<td>SCTBG</td>
<td>(1985-1991)</td>
<td>5.8</td>
</tr>
<tr>
<td>INT Milan 3</td>
<td>(1987-1989)</td>
<td>5.8</td>
</tr>
<tr>
<td>NSABP B-21</td>
<td>(1989-1998)</td>
<td>2.8</td>
</tr>
<tr>
<td>Swedish BCG 91-RT</td>
<td>1991-1997</td>
<td>4</td>
</tr>
<tr>
<td>Holli et al</td>
<td>1990-1995</td>
<td>6.3</td>
</tr>
<tr>
<td>Fyles et al</td>
<td>1992-2000</td>
<td>0.6</td>
</tr>
<tr>
<td>ABCSG study 8</td>
<td>1996-2004</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Orecchia, SGBCC, 2013
**TARGIT: Update at SABCS (December 2012)**

- 5-year cumulative risk (29 months median follow up)

<table>
<thead>
<tr>
<th></th>
<th>Targit</th>
<th>EBRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBR%</td>
<td>3.3 (23)</td>
<td>1.3 (11)</td>
<td>0.042</td>
</tr>
<tr>
<td>All LR%</td>
<td>8.2 (69)</td>
<td>5.7 (48)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Deaths%</td>
<td>3.9 (37)</td>
<td>5.3 (51)</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Intention to treatment
- EBRT in unfavourable pathology
- Over 60% in the “suitable” ASTRO group

M. Fayda  
Orecchia, SGBCC, 2013
<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>≥60</td>
<td>50–59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic factors</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm</td>
<td>≤2</td>
<td>2.1–3.0</td>
<td>&gt;3</td>
</tr>
<tr>
<td>pT</td>
<td>pT1</td>
<td>pT0 or pT2</td>
<td>pT3–pT4</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative</td>
<td>Close</td>
<td>Positive</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>LVI</td>
<td>No</td>
<td>Limited/focal</td>
<td>Extensive</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative</td>
<td>Any</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Uncentric</td>
<td>Present</td>
<td>Any</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Unifocal</td>
<td>Multifocal</td>
<td>Any</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive</td>
<td>Invasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ductal*</td>
<td>lobular</td>
<td></td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>&gt;3 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal factors</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal stage</td>
<td>pN0 (i−,i+)</td>
<td>pN0 (i−,i+)</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SNB or ALND</td>
<td>SNB or ALND</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment factors</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 3  Five-year clinical outcomes for breast cancer patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statement

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rate* (%)</td>
<td>Events</td>
</tr>
<tr>
<td>Ipsilateral breast tumor recurrence</td>
<td>3</td>
<td>1.5</td>
<td>21</td>
</tr>
<tr>
<td>Regional lymph node failure</td>
<td>3</td>
<td>1.5</td>
<td>9</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>3</td>
<td>1.5</td>
<td>8</td>
</tr>
<tr>
<td>Breast cancer related event</td>
<td>14</td>
<td>6.9</td>
<td>46</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>17</td>
<td>91.6</td>
<td>58</td>
</tr>
<tr>
<td>Cause-specific survival</td>
<td>2</td>
<td>99.1</td>
<td>7</td>
</tr>
<tr>
<td>Overall survival</td>
<td>3</td>
<td>98.6</td>
<td>13</td>
</tr>
</tbody>
</table>
Following breast conserving surgery partial breast RT may be used

- As the definitive irradiation without any external beam therapy (ASCO/ESTRO group) - 36.2%
- Only in the absence adverse tumor pathology - 40.4%
- Yes: 49, No: 22.4, Abstain: 28.6%
Comments

- **William Wood** admitted to having voted no, stating that it will be 15 years before we know the results of this technique, so he is personally not enthusiastic about it. Obviously we have good short term data and in the short term this is fine.

- **Andrew Tutt** referred to a presentation from Friday on the big variation in the way partial breast radiotherapy can be delivered both in terms of dose fractionation and volume of tissue irradiated and he thought that the answers to the questions above could be applied to one of those techniques. So he thought that a yes to that question could lead people to conclude that one of the available techniques is perfectly acceptable whereas the data are different and, for some of the techniques, the data are quite clearly inferior.
Comments

- Jay Harris added that, in the US there is a lot of controversy about how safe accelerated partial breast irradiation is using external beam radiation. Within the clinical trial the results seem to be good but recently that in a Canadian trial has seen a lot of adverse cosmetic outcomes pretty early on and the doses and volumes are very similar and so he can see why people are not completely comfortable with this approach.
Should postmastectomy RT be standard for patients with:

- N+ >3 LN?
- N+ 1-3 LN; all patients?
- N+ 1-3 LN; with adverse pathology?
- N+ 1-3 LN; young age (<40 y)?
Radiotherapy: Postmastectomy N+ 1-3 LN; all patients

British-Columbia Trial (J Natl Cancer Inst 2005) 318 pLN+ Premenopausal patients status postmodified radical mastectomy

CMF chemo alone vs. chemo + RT 20 Years RT reduced LRF (26→10%), and improved breast ca-specific survival (38→53%), and OS (37→47%)

Median 11 LN sampled

A

B

Survival (%)

Years

CT+RT

CT

p-value = 0.03 RR: 0.73 (0.55, 0.98)

Survival (%)

Years

CT+RT

CT

RR: 0.76 (0.5, 1.15)
Radiotherapy: Postmastectomy
N+ 1-3 LN; all patients

Overgaard, RO, 2007
**RT: Postmastectomy N+ 1-3 LN; with adverse pathology**

<table>
<thead>
<tr>
<th>Tumour grade</th>
<th>RT versus control</th>
<th>Absolute reduction (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>4 vs 22</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>4 vs 30</td>
<td>26 (2)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>6 vs 40</td>
<td>34 (4)</td>
</tr>
</tbody>
</table>

EBCTCG, 2005
**RT: Postmastectomy N+ 1-3 LN; young age (< 40 y)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>RT versus control</th>
<th>Absolute reduction (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>6 vs 23</td>
<td>17 (1)</td>
</tr>
<tr>
<td>50–59</td>
<td>6 vs 24</td>
<td>18 (2)</td>
</tr>
<tr>
<td>60–69</td>
<td>5 vs 23</td>
<td>18 (2)</td>
</tr>
<tr>
<td>≥70</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

(EBCTCG, 2005)
RT: Postmastectomy

Should postmastectomy RT be standard for patients with:

<table>
<thead>
<tr>
<th>Category</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Abstain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N+ (&gt;3) LN</td>
<td>95.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N+ 1-3 LN; all patients</td>
<td>29.8</td>
<td>63.8</td>
<td>6.4</td>
</tr>
<tr>
<td>N+ 1-3 LN; with adverse pathology</td>
<td>61.7</td>
<td>31.9</td>
<td>6.4</td>
</tr>
<tr>
<td>N+ 1-3 LN; young age (&lt;40 y)</td>
<td>55.1</td>
<td>40.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

A. Aydiner

13th St. Gallen IBCC, 2013
RT: Postmastectomy

Should postmastectomy RT be standard for patients with:

- pN0 after axillary dissection, but < 8 nodes examined
  - Yes: 89.1%
  - No: 4.3%
  - Abstain: 6.5%

- Positive sentinel node biopsy but no axillary dissection
  - Yes: 63.8%
  - No: 25.5%
  - Abstain: 10.6%

- Young age (<40 yr) regardless of nodes
  - Yes: 86%
  - No: 10%
  - Abstain: 4%
RT: Postmastectomy

Should postmastectomy RT be standard for patients with:
Adverse pathology regardless of nodes

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III</td>
<td>91.8</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>LVI</td>
<td>77.1</td>
<td>4.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Her2+</td>
<td>93.9</td>
<td>4.1</td>
<td>2</td>
</tr>
<tr>
<td>Triple -</td>
<td>95.7</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Aydiner, A.
RT: Postmastectomy

Should postmastectomy RT be standard for patients with:

- Tm > 5 cm regardless of nodes: 67.3% Yes, 28.6% No, 4.1% Abstain
- Positive deep/radial margins: 82.2% Yes, 11.1% No, 6.7% Abstain
Comments

- Monica Morrow remarked that the other thing that is different today is that women undergoing mastectomy with one to three nodes are not the same as women who underwent mastectomy in the trials in the pre-screening era. Now we have a lot of women who choose to have mastectomy for 5 mm cancers with a very low nodal disease burden and so it is also not clear if the benefit is the same.

- Jay Harris noted that there are patients in whom we only treat the chest wall but there is growing comfort in just treating the chest wall in selected patients at risk, primarily for chest wall recurrence.
Radiotherapy (RT)

- There is a group not requiring RT as part of BCT.
- Short course RT (e.g. 40 Gy in 15 fractions) be offered as a standard in some patients, and is an option if boost is also planned.
- Following breast conserving surgery partial breast RT may be used only in the absence of adverse tumor pathology.

- Postmastectomy RT be standard for patients with,
  1. LN > 3 positive.
  2. LN 1-3 positive, with adverse pathology
  3. LN 1-3 positive in young age (< 40)

Postmastectomy RT should not be standard for patients with adverse pathology (like Her2, grade) regardless of nodes.
Postmastectomy RT should be standard for patients with tm > 5 cm (regardless of nodes) or with positive deep/radial margins.
Radiotherapy (RT)

Nodal areas requiring RT should:

- Include supraclavicular fossa in all irradiated patients: 32.7% Yes, 53.1% No, 14.3% Abstain
- Include axilla in all irradiated patients: 6.8% Yes, 81.8% No, 11.4% Abstain
- Include internal mammary nodes in all irradiated patients: 10.9% Yes, 69.6% No, 19.6% Abstain
Should nodal areas requiring RT be influenced by response to neoadjuvant therapy?
Not RANDOMIZED DATA

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27


See accompanying editorial on page 3913 and article on page 3916
### Table 1. Rates of Locoregional Recurrence After Mastectomy in NSABP B-18 and B-27

<table>
<thead>
<tr>
<th>Lymph Node Stage at Presentation</th>
<th>Tumor Size at Presentation (cm)</th>
<th>Residual Invasive Tumor After Preoperative Chemotherapy</th>
<th>No. of Patients in Each Subset</th>
<th>10-Year Cumulative Incidence of LRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 5</td>
<td>Breast − Lymph Node −</td>
<td>46</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ −</td>
<td>178</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any −</td>
<td>184</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>&gt; 5</td>
<td>− −</td>
<td>16</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ −</td>
<td>95</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any −</td>
<td>179</td>
<td>14.6</td>
</tr>
<tr>
<td>Clinically node positive</td>
<td>≤ 5</td>
<td>Breast − Lymph Node −</td>
<td>21</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ −</td>
<td>37</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any −</td>
<td>143</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>&gt; 5</td>
<td>− −</td>
<td>11</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any −</td>
<td>33</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>128</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Abbreviations: LRR, locoregional recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project.
• **NSABP-RTOG 9353**
  - T1-3 N1 [nodal mets confirmed with FNA]
  - ypN0 found at axillary dissection after neoadjuvant chemo.
    • Post BCS → Breast RT vs. Breast + regional RT
    • Post MRM → observ. vs. PMRT

• **A011202 (ACOSOG + CALGB+NCCTG)**
  - T1-3 N1
  - ypN+ found at SLNB after neoadjuvant chemo.
    • All pts will get breast/Chest wall + none dissected supra- level 3 RT.
      → Axillary dissection vs. axillary RT
Radiotherapy

Nodal areas requiring RT should:

- Be influenced by response to neoadjuvant therapy
  - Yes: 33.3%
  - No: 55.6%
  - Abstain: 11.1%

- Be influenced by the intrinsic subtype of the tumor
  - Yes: 16.7%
  - No: 77.1%
  - Abstain: 6.3%
Comments

- **Sibylle Loibl** added that nodal radiotherapy should not be influenced by the response to neoadjuvant therapy. We do not have much data in this area and perhaps we need to reflect that in a patient with pCR maybe the nodes do not need to be irradiated. Another panelist added that we have recent clinical trial data addressing this point.

- **Partridge** commented that young age, given the uncertainty over whether this will remain a prognostic and predictive factor, is one factor we take into account when thinking about the need for post-mastectomy irradiation and because they have the highest risk of locoregional recurrence.
Comments

Alan Coates added that, as we move on to pathology in this process, we have seen that the local therapists are not too keen on changing their treatment based on pathology. But that is not the case when we come to think about systemic therapy. The real areas where we need to progress this time are in the areas of luminal disease that is HER-2 negative and there we have a great deal to look at. We now have ample evidence that you can look for prognostic factors and most of the tests you can look at will give you prognostic information. More important is the predictive scale, what he refers to as the chemofutility axis - are there patients, even though they may be at risk, for whom chemotherapy simply does not work. That's a very different question, it is a predictive question and the evidence for this is strong. If chemotherapy adds nothing then we are going to need labels within this space of luminal HER-2 negative disease. He would prefer to keep something that refers to the underlying types and we need to keep in mind that the ultimate reason for exploring this space is to give or withhold toxic chemotherapy.

Eric Winer added that surgeons and radiation oncologists are right to consider biology to help them change their treatments but they just don't know how to do it yet. We are seeing the struggle to incorporate biology in the decision making process.
Conference Topic

Pathology
Pathology

For practical purposes distinction between clinical luminal A and Luminal B (Her 2-) tumors can be:

- Made by ER, PR alone: 91.8% Yes, 6.1% No, 2% Abstain
- Made by ER, PR and Ki 67: 72.9% Yes, 27.1% No, 0% Abstain
- Made with grade 3 as a substitute for high Ki-67: 64% Yes, 36% No, 0% Abstain
- Only safely determined by molecular diagnostics: 60% Yes, 34% No, 6% Abstain
- Only safely determined by laboratories with QAP: 88.9% Yes, 8.9% No, 2.2% Abstain

QAP - quality assurance program
Breast Cancer Subtypes

Normal mammary development

Breast tumor subtype

Signatures

Stem cell (MaSC)

Bipotent progenitor

Myoepithelial progenitor

Differentiated myoepithelial cells

Differentiated luminal cells

Claudin-low

Basal-like

BRCA1 mutation

Late luminal progenitor

HER2 amplicon

HER2-enriched

Luminal B

Luminal A

Mesenchymal

Basal-like

“Triple Negative” -- a mixture of subtypes

HER2 and ER can be expressed in any subtype....

### St. Gallen 2011: “Shorthand” Determination of Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Surrogate Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER and/or PgR(+), HER2(-)</td>
</tr>
<tr>
<td></td>
<td>Ki-67 low (&lt;14%)*</td>
</tr>
<tr>
<td>Luminal B1</td>
<td>ER and/or PgR(+), HER2(-)</td>
</tr>
<tr>
<td></td>
<td>Ki-67 high</td>
</tr>
<tr>
<td>Luminal B2</td>
<td>ER and/or PgR(+), HER2(+)</td>
</tr>
<tr>
<td></td>
<td>Any Ki-67</td>
</tr>
<tr>
<td>HER2 over-expression</td>
<td>ER and PgR absent, HER2(+)</td>
</tr>
<tr>
<td>Basal-like</td>
<td>Triple negative ductal (not medullary, adenoid cystic)</td>
</tr>
</tbody>
</table>

* Using PAM50 cutpoint from Cheang et al. JNCI 2009

In the determination of Her2 status for anti Her2 treatment purposes, do we need to know:

- Yes
- No
- Abstain

Aydiner
Pathology: HER2

For treatment decisions do we also need to know

- Concomittant estrogen receptor expression status: Yes 40.5%, No 59.5%
- Degree of tumor proliferation: Yes 0%, No 10.4%, Abstain 89.6%
Pathology: Subtypes

Does intrinsic subtype may influence whether or not chemotherapy is used in the adjuvant regimen?

- Yes: 88.9%
- No: 6.7%
- Abstain: 4.4%
Pathology: Subtypes

Multigene expression array profiling is required for subtype definition

Clinicopathologic definition of subtype (e.g. St Gallen 2011) is sufficient for this purpose

Yes  No  Abstain
Pathology: Subtypes

Choice of cytotoxic chemotherapy regimen should be influenced by intrinsic subtype? (whether you get anthracycline vs no etc)

- Yes: 27.7%
- No: 68.1%
- Abstain: 4.3%
A Theoretical Spectrum of Sensitivity to Adjuvant Systemic Therapy by Intrinsic Subtypes

Hayes DF. Journal of Clinical Oncology, 30(12):1264-1267, 2012
# Systemic treatment recommendations

<table>
<thead>
<tr>
<th>'Subtype'</th>
<th>Type of therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Luminal A'</td>
<td>Endocrine therapy alone</td>
<td>Few require cytotoxics (e.g. high nodal status).</td>
</tr>
<tr>
<td>‘Luminal B (HER2 negative)’</td>
<td>Cytotoxics ± endocrine therapy</td>
<td>Inclusion and type of cytotoxics may depend on level of endocrine expression, perceived risk and patient preference.</td>
</tr>
<tr>
<td>‘Luminal B (HER2 positive)’</td>
<td>Cytotoxics + anti-HER2+ endocrine therapy</td>
<td>No data are available to support the omission of cytotoxics in this group.</td>
</tr>
<tr>
<td>‘HER2 positive (non luminal)’</td>
<td>Cytotoxics + anti-HER2</td>
<td>Patients at very low risk may be observed without treatment</td>
</tr>
<tr>
<td>‘Triple negative (ductal)’</td>
<td>Cytotoxics</td>
<td></td>
</tr>
<tr>
<td>'Special histological types'*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Endocrine responsive</td>
<td>Endocrine therapy</td>
<td></td>
</tr>
<tr>
<td>B. Endocrine non responsive</td>
<td>Cytotoxics</td>
<td>Medullary and apocrine carcinomas may not require any adjuvant cytotoxics (if node negative).</td>
</tr>
</tbody>
</table>

The Recurrence Score® Results Uses Key Genes Linked to Critical Molecular Pathways

16 Breast Cancer Related Genes

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Proliferation</th>
<th>HER2</th>
<th>Invasion</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER PR Bcl2 SCUBE2</td>
<td>Ki-67 STK15 Survivin Cyclin B1 MYBL2</td>
<td>GRB7 HER2</td>
<td>Stromelysin 3 Cathepsin L2</td>
<td>CD68 GSTM1 BAG1</td>
</tr>
</tbody>
</table>

5 Reference Genes

- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

NSABP B-20: Significant proportion of high-grade tumors have a low Recurrence Score® result and many low-grade tumors have a high result.

Recurrence Score® by Ki-67

Standard Cut-offs

- **high risk** (≥31)
- **intermediate risk** (18-30)
- **low risk** (<18)

Ki-67 <14  Ki-67 ≥14  Ki-67 <20  Ki-67 ≥20

3%  19%  3%  26%
36%  43%  38%  44%
61%  38%  59%  30%
**Oncotype DX® Is the Only Multigene Expression Assay Incorporated into NCCN®, ASCO®, and St. Gallen’s Guidelines**

**NCCN Guidelines™**
- Consider use in > 0.5 cm, HR+, HER2– disease
- pT1, pT2, or pT3 and pN1mi (≤ 2 mm axillary node metastasis)

**ASCO Guidelines**
- Newly diagnosed patients with node-negative, ER+ breast cancer who will receive tamoxifen

**St. Gallen 2011 Consensus**
- Oncotype DX has been shown to predict chemotherapy benefit among patients with HR+ disease
Multi-Gene Signatures

Would you ask for one of multigene signatures (after clinicopathologic assessment)?

- In nearly all cases independently of the intrinsic subtype: 97.6%
- In nearly all ER and/or PR+ (Her2-) cases: 79.2%
- In nearly all Luminal B (Her2-) but not Luminal A cases: 51.1%
- In node negative, ER+ and Her2 negative cases: 43.2%
- In node positive, Her2 negative cases: 77.8%

Options:
- Yes
- No
- Abstain
Multi-Gene Signatures

In an endocrine responsive* cohort:

- Does 21 RS predict CT response?
  - Yes: 78
  - No: 12
  - Abstain: 10

- Does PAM-50 predict CT response?
  - Yes: 29,5
  - No: 40,9
  - Abstain: 29,5

- Does 70 gene signature predict CT response?
  - Yes: 25
  - No: 54,2
  - Abstain: 20,8

- Does EPcline predict CT response?
  - Yes: 10,6
  - No: 57,4
  - Abstain: 31,9

* i.e. Any expression of ER and/or PR
Comments

- **Jay Harris** stated that regarding the actual assays, there remains a lot of variability for example it would be a tremendous mistake for this panel to recommend that Ki67 done by IHC should be used to determine whether or not chemotherapy should or should not be given.

- **Martine Piccart** also added that the Ki67 is an unreliable assay we should not make recommendations for women based on this assay that has no demonstration of analytical validity. Perhaps a compromise is in grade III tumour where you can be relatively confident in Ki67 but for all the other tumours Ki67 is not the right way to go right now.
Comments

- Pathologist Frederique Penault-Llorca's perspective is that we should try to have agreement on the percentage through quality assurance procedures. Overall, we can manage to do Ki67 even though it is imperfect (particularly in the range 20-30%). We are not very good with grade II tumours, that's a fact, but we do actually have good reproducibility for grade III tumours (i.e. those with high Ki67 expression).

- Eric Winer concluded that it is important to look at the pathology report with a healthy dose of skepticism - particular the results of any single test. We will be a place in a few years to offer much more precise diagnostics. We are now training molecular pathology and we are far beyond the morphological diagnosis.
Multi-Gene Signatures

In an endocrine responsive* cohort, selection of patients who might forego chemotherapy can be partially based on:

Aydiner

* i.e. Any expression of ER and/or PR
In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because

* i.e. Any expression of ER and/or PR
Molecular Diagnostics

In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because

- Yes: 93.8%
- No: 4.2%
- Abstain: 2.1%

* i.e. Any expression of ER and/or PR
Molecular Diagnostics

In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because

1-3 nodes positive

- Yes: 26.3%
- No: 71.1%
- Abstain: 2.6%

4 or more nodes positive

- Yes: 91.5%
- No: 6.4%
- Abstain: 2.1%

* i.e. Any expression of ER and/or PR
Molecular Diagnostics

In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>30.6</td>
<td>65.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Low ER (eg % 5)</td>
<td>55.8</td>
<td>44.2</td>
<td>0</td>
</tr>
<tr>
<td>Young age (eg &lt; 35)</td>
<td>24.4</td>
<td>75.6</td>
<td>0</td>
</tr>
</tbody>
</table>

* i.e. Any expression of ER and/or PR
Pathologic features of the stroma which should influence therapy choice in routine clinical practice include:

- Immunocyte infiltration: 74.3% Yes, 14.3% No, 11.4% Abstain
- Microvascular dusty: 88.1% Yes, 2.1% No, 9.5% Abstain
- Stromal P16 stain: 97.7% Yes, 2.3% No, 0% Abstain
For practical purposes distinction between luminal A and Luminal B (Her 2 -) tumors can be made by ER, PR, Ki67, and only determined by laboratories with quality assurance program.

In the determination of Her2 status for anti Her2 treatment purposes, we do not need to know heterogenity of over expression of Her2.

In Her2 positive patients estrogen receptor status, and degree of tumor proliferation do not change treatment decisions.
Intrinsic subtype may influence whether or not chemotherapy is used in the adjuvant regimen.

Multigene expression array profiling is not required for subtype definition. Clinicopathologic definition of subtype (e.g. St Gallen 2011) is sufficient for this purpose.

Choice of cytotoxic chemotherapy regimen should not be influenced by intrinsic subtype.
PATHOLOGY 3

- We would ask for one of multigene signatures (after clinicopathologic assessment) in node negative, ER + and Her2 – cases.
- In an endocrine responsive cohort, 21 gene RS (OncotypeDx) predicts chemotherapy response and selection of patients who might forego chemotherapy can be partially based on this result.
- In an endocrine responsive cohort, if ‘tm < 1cm and node negative’, inflammatory breast cancer, 4 or more + LN, low ER (e.g. %5)molecular diagnostics can be omitted.
Conference Topic

Endocrine therapy
Endocrine Therapies
Establishing Standards for Premenopausal

Tamoxifen alone as default (in ER +)

83.3% Yes
16.7% No
0% Abstain
Endocrine Therapies
Establishing Standards for Premenopausal

Tamoxifen duration should be extended to 10 years

- In most patients remaining premenopausal: 42.9% (Yes), 49% (No), 8.2% (Abstain)
- In some patients remaining premenopausal: 88.9% (Yes), 8.9% (No), 2.2% (Abstain)
## Extended Tamoxifen 5 vs 10 Years - ATLAS

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of ER-Positive Patients (%)</th>
<th>Factor</th>
<th>Ratio of Annual Event Rates (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 45 yr</td>
<td>1270 (19%)</td>
<td>Age &lt; 55 yr</td>
<td>0.83 (0.07)</td>
</tr>
<tr>
<td>Age 45-54 yr</td>
<td>2189 (32%)</td>
<td>Age ≥ 55yr</td>
<td>0.86 (0.07)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>630 (10%)</td>
<td>Premenopausal</td>
<td>0.81 (0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post/unknown</td>
<td>0.85 (0.05)</td>
</tr>
</tbody>
</table>

Davies et al, 2013
Endocrine Therapies
Establishing Standards for Premenopausal

Ovarian function suppression (OFS) should be added to tamoxifen

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Young (eg 40 &lt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>80.9%</td>
<td>50.0%</td>
</tr>
<tr>
<td>No</td>
<td>14.9%</td>
<td>40.9%</td>
</tr>
<tr>
<td>Abstain</td>
<td>4.3%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

OFS - Ovarian function suppression
Endocrine Therapies
Establishing Standards for Premenopausal

OFS alone (without tamoxifen) | AI + OFS is a valid option in case of contrindication to tamoxifen | AI + OFS is a valid option in all cases
---|---|---
24 Yes | 85 | 1 Yes | 87 | 5
70 No | 8 | 5 No | 6 | 4 Abstain | 6 | 3 Abstain | 6 | 3

OFS - Ovarian function supression
Optimal Endocrine Therapy For Premenopausal Women ABCSG12

- Accrual 1999-2006
- 1803 premenopausal breast cancer patients
- Endocrine – responsive (ER and / or PR positive)
- Stage I & II, < 10 positive nodes
- Neoadjuvant chemo only
- Treatment duration: 3 years

Surgery (+RT) → Goserelin 3.6 mg q28d → Randomize 1:1:1:1 →

- Tamoxifen 20 mg/d
- Tamoxifen 20 mg/d + Zoledronic acid 4 mg q6m
- Anastrozole 1 mg/d
- Anastrozole 1 mg/d + Zoledronic acid 4 mg q6m

Gnant et al NEJM 2009
Worse OS but not RFS with AI in ABCSG12 at 62 Months Median Follow-up

<table>
<thead>
<tr>
<th>DFS</th>
<th>1.08 (0.81-1.44) p=0.591</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>1.75 (1.08-2.83) p=0.02</td>
</tr>
</tbody>
</table>

- Why?
- 96% of women enrolled are alive
- No clear explanation
- No obvious differences in cause of death
- Chance? Methods? Inadequate salvage?
- Role of obesity?

Neoadjuvant Combined Endocrine Therapy - STAGE

Pre-menopausal Receptor-positive Her2-negative Operable N=197

Goserelin + anastrozole + placebo (GAP)  
RR 70%

Goserelin + tamoxifen + placebo (GTP)  
RR 51%

Masuda et al, Lancet Oncol, 2012
Endocrine Therapies
Establishing Standards for Postmenopausal

Can some patients be adequately treated with tamoxifen alone?

- Yes: 93.6%
- No: 6.4%
- Abstain: 0%

A. Aydiner
Review

Meta-analysis of breast cancer outcome and toxicity in adjuvant trials of aromatase inhibitors in postmenopausal women

Adnan Aydiner*

Istanbul University, Institute of Oncology, 34390 Istanbul, Turkey
Table 2
Effect estimates of the individual randomized controlled trials (RCTs) and the meta-analysis for AI monotherapy versus 5 yrs of tamoxifen treatment.

<table>
<thead>
<tr>
<th>RCT reference</th>
<th>Intervetion arm</th>
<th>DFS [HR (95% CI)]</th>
<th>OS [HR (95% CI)]</th>
<th>DWR [HR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RCT</td>
<td>Meta-analysis</td>
<td>RCT</td>
</tr>
<tr>
<td>Overall,</td>
<td>Anastrozole 5 yrs</td>
<td>0.91 (0.83–0.99)</td>
<td><strong>0.89 (0.83–0.95)</strong></td>
<td>p = 0.001</td>
</tr>
<tr>
<td>ATAC (follow-up: 120 mo)</td>
<td>Letrozole 5 yrs</td>
<td>0.86 (0.77–0.95)</td>
<td>0.87 (0.76–0.99)</td>
<td>1.00 (0.74–1.35)</td>
</tr>
<tr>
<td>BIG 1—98 (Hormone receptor-positive)</td>
<td>Anastrozole 5 yrs</td>
<td>0.86 (0.78–0.95)</td>
<td><strong>0.86 (0.8–0.92)</strong></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ATAC (follow-up: 120 mo)</td>
<td>Letrozole 5 yrs</td>
<td>0.86 (0.77–0.95)</td>
<td>0.87 (0.76–0.99)</td>
<td>1.00 (0.74–1.35)</td>
</tr>
</tbody>
</table>

CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; OS: overall survival; DWR: death without recurrence; R: receptor.
### A

<table>
<thead>
<tr>
<th>RCT reference</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>0.91</td>
<td>0.83</td>
<td>0.99</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>0.86</td>
<td>0.77</td>
<td>0.95</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.89</td>
<td>0.83</td>
<td>0.95</td>
</tr>
<tr>
<td>Overall, survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>0.97</td>
<td>0.87</td>
<td>1.08</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>0.87</td>
<td>0.76</td>
<td>0.99</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.93</td>
<td>0.83</td>
<td>1.03</td>
</tr>
<tr>
<td>Death without recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>0.97</td>
<td>0.87</td>
<td>1.08</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>1.00</td>
<td>0.74</td>
<td>1.35</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.97</td>
<td>0.88</td>
<td>1.07</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; HR: hazard ratio; 95% CI: lower and upper boundaries of the 95% confidence interval; AI: aromatase inhibitor
### Table: Meta-analysis and Individual Trials

<table>
<thead>
<tr>
<th>RCT Reference</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
<th>Death without recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>P</strong></td>
<td><strong>HR</strong></td>
</tr>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>0.86</td>
<td>0.78</td>
<td>0.95</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>0.86</td>
<td>0.77</td>
<td>0.95</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.86</td>
<td>0.80</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>0.95</td>
<td>0.85</td>
<td>1.06</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>0.87</td>
<td>0.76</td>
<td>0.99</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.92</td>
<td>0.84</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Death without recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC(^{18})</td>
<td>1.04</td>
<td>0.88</td>
<td>1.22</td>
</tr>
<tr>
<td>BIG 1-98(^{19,20})</td>
<td>1.00</td>
<td>0.74</td>
<td>1.35</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1.03</td>
<td>0.89</td>
<td>1.19</td>
</tr>
</tbody>
</table>

- **RCT**: randomized controlled trial; **HR**: hazard ratio; **95% CI**: lower and upper boundaries of the 95% confidence interval; **AI**: aromatase inhibitor.
<table>
<thead>
<tr>
<th>RCT reference</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 8+ ARNO-95</td>
<td>0.60</td>
<td>0.44-0.81</td>
<td>0.001</td>
</tr>
<tr>
<td>TEAM</td>
<td>0.68</td>
<td>0.56-0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N-SAS BC03</td>
<td>0.60</td>
<td>0.42-1.14</td>
<td>0.145</td>
</tr>
<tr>
<td>ITA</td>
<td>0.57</td>
<td>0.38-0.85</td>
<td>0.006</td>
</tr>
<tr>
<td>IE Study</td>
<td>0.76</td>
<td>0.66-0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARNO 95</td>
<td>0.66</td>
<td>0.44-0.99</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td><strong>0.70</strong></td>
<td><strong>0.63-0.77</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Overall, survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 8+ ARNO-95</td>
<td>0.76</td>
<td>0.51-1.12</td>
<td>0.160</td>
</tr>
<tr>
<td>TEAM</td>
<td>0.88</td>
<td>0.67-1.16</td>
<td>0.361</td>
</tr>
<tr>
<td>N-SAS BC03</td>
<td>0.82</td>
<td>0.24-2.84</td>
<td>0.757</td>
</tr>
<tr>
<td>ITA</td>
<td>0.56</td>
<td>0.28-1.13</td>
<td>0.108</td>
</tr>
<tr>
<td>IE Study</td>
<td>0.85</td>
<td>0.71-1.02</td>
<td>0.079</td>
</tr>
<tr>
<td>ARNO 95</td>
<td>0.53</td>
<td>0.28-1.00</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td><strong>0.81</strong></td>
<td><strong>0.71-0.93</strong></td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td><strong>Distant metastasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 8+ ARNO-95</td>
<td>0.61</td>
<td>0.42-0.88</td>
<td>0.008</td>
</tr>
<tr>
<td>TEAM</td>
<td>0.66</td>
<td>0.52-0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N-SAS BC03</td>
<td>0.59</td>
<td>0.29-1.20</td>
<td>0.146</td>
</tr>
<tr>
<td>ITA</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IE Study</td>
<td>0.83</td>
<td>0.70-0.98</td>
<td>0.031</td>
</tr>
<tr>
<td>ARNO 95</td>
<td>0.84</td>
<td>0.51-1.40</td>
<td>0.511</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td><strong>0.74</strong></td>
<td><strong>0.65-0.85</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>
### Disease-free survival

<table>
<thead>
<tr>
<th>RCT Reference</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG 6a</td>
<td>0.62</td>
<td>0.40</td>
<td>0.96</td>
</tr>
<tr>
<td>MA.17</td>
<td>0.57</td>
<td>0.43</td>
<td>0.75</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>0.68</td>
<td>0.51</td>
<td>0.90</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.62</td>
<td>0.52</td>
<td>0.74</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th>RCT Reference</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG 6a</td>
<td>0.89</td>
<td>0.59</td>
<td>1.34</td>
</tr>
<tr>
<td>MA.17</td>
<td>0.76</td>
<td>0.48</td>
<td>1.21</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>1.15</td>
<td>0.55</td>
<td>2.38</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.87</td>
<td>0.66</td>
<td>1.16</td>
</tr>
</tbody>
</table>

### Distant metastasis

<table>
<thead>
<tr>
<th>RCT Reference</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG 6a</td>
<td>0.53</td>
<td>0.29</td>
<td>0.96</td>
</tr>
<tr>
<td>MA.17</td>
<td>0.64</td>
<td>0.45</td>
<td>0.91</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>0.67</td>
<td>0.32</td>
<td>1.43</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.62</td>
<td>0.46</td>
<td>0.82</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; HR: hazard ratio; 95% CI: lower and upper boundaries of the 95% confidence interval; AI: aromatase inhibitor
Conclusions

- DFS was significantly improved by AI monotherapy, sequenced therapy and extended therapy.
- All of the patients benefited significantly from sequenced therapy.
- Hormone receptor positive patients benefited from AI monotherapy with respect to OS
- Safety analyses
  - AI monotherapy conferred significantly lower risks for thromboembolic events and endometrial cancer compared with tamoxifen monotherapy; however, there was a greater risk of cardiovascular events.
  - Sequenced therapy was also superior in terms of endometrial cancer but was inferior with respect to fractures, thromboembolic and cardiovascular events.
Endocrine Therapies
Establishing Standards for Postmenopausal

If an aromatase inhibitor, need it be started upfront

- In all patients (≈90% of pts):
  - Yes: 47.5
  - No: 50
  - Abstain: 2.5

- In high risk patients:
  - Yes: 87.2
  - No: 10.7
  - Abstain: 2.1
Endocrine Therapies
Establishing Standards for Postmenopausal

Can upfront aromatase inhibitor be replaced with tamoxifen after 2 years?

- Yes: 68.1%
- No: 29.8%
- Abstain: 2.1%
Endocrine Therapies
Establishing Standards for Postmenopausal

Should extended aromatase inhibitor beyond 5 years of adjuvant endocrine treatment be offered to patients with:

- Node positive disease:
  - Yes: 57.8%
  - No: 17.8%
  - Abstain: 24.4%

- Node negative disease:
  - Yes: 66%
  - No: 25.6%
  - Abstain: 8.5%
Endocrine Therapies
Establishing Standards for Postmenopausal

If so, does prior endocrine therapy matter? Should extend AI beyond 5 years be given after:

- 5 yrs adjuvant tamoxifen
  - Yes: 83.3%
  - No: 11.9%
  - Abstain: 4.8%

- 5 yrs endocrine therapy switching from tamoxifen to AI.
  - Yes: 73.3%
  - No: 11.1%
  - Abstain: 15.6%

- 5 yrs adjuvant AI
  - Yes: 35.6%
  - No: 40%
  - Abstain: 24.4%
Endocrine Therapies
Establishing Standards for Postmenopausal

If AI is unavailable or not tolerated (to switch to tamoxifen), should tamoxifen be continued beyond 5 years.

- Yes: 78
- No: 8
- Abstain: 14
Endocrine Therapies
Establishing Standards for Postmenopausal

After 5 yrs AI, should you consider putting her on TAM at 5 yrs
- Yes: 51.1%
- No: 28.9%
- Abstain: 20%

After 5 yrs AI, do you tell her to take tamoxifen
- Yes: 48.6%
- No: 31.4%
- Abstain: 20%
Tamoxifen as default (in ER +)
Tamoxifen duration should be extended to 10 years in some patients remaining premenopausal
Ovarian function supression (OFS) should not be added to tamoxifen in all patients, may be added in the young (eg < 40).
Aİ+OFS is a valid option in case of contraindication to tamoxifen
Some patients can be adequately treated with tamoxifen alone.
- If an aromatase inhibitor, it needs to be started upfront in high risk patients
- Upfront aromatase inhibitor can be replaced with tamoxifen after 2 years
ENDOCRINE THERAPIES

- Extended aromatase inhibitor beyond 5 years of adjuvant endocrine treatment should be offered to patients with node positive disease
- If AI is unavailable or not tolerated (to switch to tamoxifen), tamoxifen should be continued beyond 5 years
- After 5 yrs AI, tamoxifen should be considered any time
Chemotherapy
Chemotherapy

Factors arguing inclusion of chemotherapy are (basic):

- Histologic grade 3 tumor: Yes 84.4%, No 13.3%, Abstain 2.2%
- Ki 67 high: Yes 75.5%, No 14.3%, Abstain 10.2%
- Low hormone receptor: Yes 81.6%, No 8.2%, Abstain 0%
Chemotherapy

Factors arguing inclusion of chemotherapy are (basic):

- Positive Her2 status: 91.8% Yes, 8.2% No, 0% Abstain
- Triple negative disease: 98% Yes, 0% No, 2% Abstain
Factors arguing inclusion of chemotherapy are:

- **High 21 gene RS (eg > 25)**:
  - Yes: 93.9%
  - No: 4.1%
  - Abstain: 2%

- **70 gene high risk**:
  - Yes: 63.3%
  - No: 30.6%
  - Abstain: 6.1%
Factors arguing inclusion of chemotherapy are:

Any positive node: 32.7%

> 3 positive nodes: 67.3%

Yes
No
Abstain
Chemotherapy

Factors arguing inclusion of chemotherapy are:

- Lymphovascular invasion: 32 Yes, 64 No
- Young age (eg < 35 y): 46 Yes, 54 No

Legend: Green = Yes, Red = No, Yellow = Abstain
Factors arguing inclusion of chemotherapy are:
- histologic grade 3 tumor,
- high Ki67,
- low ER,
- positive Her2 status,
- triple negative disease,
- high 21 gene RS (eg > 25)
- ≥ 4 positive nodes
Chemotherapy

Is luminal A phenotype less responsive to CT?

- Yes: 83.3%
- No: 10.4%
- Abstain: 6.3%

A. Aydiner
Chemotherapy

Is less intensive CT such as AC4 or CMF 6 or TC4 adequate if CT is considered in Luminal A disease?

- Yes: 61.7%
- No: 25.5%
- Abstain: 12.8%
Chemotherapy

Should CT be added for high risk based on tumor volume (size, nodes)?

- Yes: 60
- No: 22.9
- Abstain: 17.1
# Systemic treatment recommendations

<table>
<thead>
<tr>
<th>‘Subtype’</th>
<th>Type of therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Luminal A’</td>
<td>Endocrine therapy alone</td>
<td>Few require cytotoxics (e.g. high nodal status).</td>
</tr>
<tr>
<td>‘Luminal B (HER2 negative)’</td>
<td>Cytotoxics + endocrine therapy</td>
<td>Inclusion and type of cytotoxics may depend on level of endocrine expression, perceived risk and patient preference.</td>
</tr>
<tr>
<td>‘Luminal B (HER2 positive)’</td>
<td>Cytotoxics + anti-HER2+ endocrine therapy</td>
<td>No data are available to support the omission of cytotoxics in this group.</td>
</tr>
<tr>
<td>‘HER2 positive (non luminal)’</td>
<td>Cytotoxics + anti-HER2</td>
<td>Patients at very low risk may be observed without treatment</td>
</tr>
<tr>
<td>‘Triple negative (ductal)’</td>
<td>Cytotoxics</td>
<td></td>
</tr>
<tr>
<td>‘Special histological types*’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Endocrine responsive</td>
<td>Endocrine therapy</td>
<td></td>
</tr>
<tr>
<td>B. Endocrine non responsive</td>
<td>Cytotoxics</td>
<td>Medullary and apocrine carcinomas may not require any adjuvant cytotoxics (if node negative).</td>
</tr>
</tbody>
</table>

*Goldhirsch A. Annals Oncol 2011, doi:10.1093/annonc/mdr304*
More Data for Selecting TYPE of Adjuvant Chemotherapy for ER+ “Luminal” Breast Cancer

- Central IHC for ER, HER2 – CALGB 9344
  No benefit to paclitaxel after AC (vs AC) if ER+/HER2-

- Central IHC for ER, HER2, Ki67 – BCIRG 001
  No benefit to TAC (vs FAC) if ER+/HER2-/Ki67 low

- PAM50 – NCIC MA.5
  No benefit to CEF (Vs CMF) in either Luminal A or Luminal B

- ClinPath, PAM50, PAM50 proliferation – GEICAM 9906
  Benefit to paclitaxel after FEC (vs FEC only low PAM50 proliferation

Albain KS, St Gallen 2013
Luminal A phenotype is less responsive to CT
Less intensive CT, such as AC4 or CMF 6 or TC4 are adequate if CT is considered in Luminal A disease
CT should be added for high risk based on tm volume (e.g. size, nodes)
Is luminal B subtype by itself sufficient to prescribe CT?

- Yes: 61.2%
- No: 38.8%
- Abstain: 0%
Chemotherapy
Luminal B HER2 (-)

Is Ki67 useful in defining luminal B subtype?

- Yes: 72.9%
- No: 20.8%
- Abstain: 6.3%
Chemotherapy
Luminal B HER2 (-)

If Ki67 is used, which threshold should be used for defining luminal B subtype (Her 2 -)?

- Yes: 23.9
- No: 37
- Abstain: 39.1

- Yes: 29.5
- No: 13.6
- Abstain: 56.8

- Yes: 13.3
- No: 6.7
- Abstain: 80

≥14%
≥20%
≥25%
Chemotherapy
Luminal B HER2 (-)

If given CT regimen should contain antracycline rather than CMF?

- Yes: 70.5%
- No: 18.2%
- Abstain: 11.4%
Chemotherapy
Luminal B HER2 (-)

Should the regimen contain taxanes?

56.5% yes
26.1% no
17.4% abstain
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Overall mortality
11,167 women
RR 0.86 (95% CI 0.79–0.93)
Log-rank 2p=0.0002
8-year gain 3.2% (SE 0.9)

33,084 women
RR 0.90 (95% CI 0.84–0.97)
Log-rank 2p=0.008
5-year gain 1.2% (SE 0.5)

Aydiner
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Breast cancer mortality
8575 women
RR 0.79 (95% CI 0.72–0.85)
Log-rank 2p < 0.00001
10-year gain 6.5% (SE 1.2)
No CTX 35.8%
29.3% Anthracycline
21.0%
15.9%

5253 women
RR 0.76 (95% CI 0.68–0.84)
Log-rank 2p < 0.00001
10-year gain 6.2% (SE 1.3)
No CTX 27.6%
21.5% CMF
15.3%
11.8%

Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses


A. Aydiner
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Overall mortality
8575 women
RR 0.84 (95% CI 0.78–0.91)
Log-rank 2p = 0.00001
10-year gain 5.0% (SE 1.2)

Any death (%)

No CTX
39.6%
34.6%
Anthracycline

23.1%
18.0%

Years
Death rates (%/year) and log-rank analyses

5253 women
RR 0.84 (95% CI 0.76–0.93)
Log-rank 2p = 0.0004
10-year gain 4.7% (SE 1.3)

No CTX
30.7%
26.0%
CMF

16.4%
13.7%

Years
Death rates (%/year) and log-rank analyses

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

ER status

2076 women, ER-poor (73% N+)

Control

41.9%

Anthracycline

34.8%

28.3%

22.9%

RR 0.80 (95% CI 0.69–0.93)

Log-rank 2p=0.003

10-year gain 7.1% (SE 2.3)

5433 women, ER+ (86% N+)

Control

32.0%

Anthracycline

25.6%

16.7%

12.2%

RR 0.77 (95% CI 0.69–0.86)

Log-rank 2p<0.00001

10-year gain 6.4% (SE 1.4)

Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

**ER+ disease only: entry age <55 or 55–69 years**

1582 women, ER+, age <55 (77% N+)

RR 0.83 (95% CI 0.68–1.00)

Log-rank 2p=0.05

10-year gain 5.6% (SE 2.6)

- Control 33.7%
- Anthracycline 28.1%

**3578 women, ER+, age 55–69 (90% N+)**

RR 0.78 (95% CI 0.68–0.89)

Log-rank 2p=0.0002

10-year gain 6.0% (SE 1.8)

- Control 31.0%
- Anthracycline 25.0%

Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Chemotherapy
Luminal B HER2 (-)

Should CT extend for at least 6 courses?

- Yes: 50
- No: 34.8
- Abstain: 15.2

A. Aydiner
Chemotherapy
Luminal B HER2 (-)

Should dose dense CT be preferred when CT indicated?

- Yes: 19.1%
- No: 68.1%
- Abstain: 12.8%
CHEMOTHERAPY
LUMINAL B HER2 (-)

- Luminal B subtype by itself is sufficient to prescribe CT
- Ki67 is useful in defining luminal B subtype
- If Ki67 is used, higher than %20 should be used as threshold for defining luminal B subtype
- If given, CT regimen should contain antracycline and taxane rather than CMF
- CT should extend for at least 6 courses
Chemotherapy
Luminal B HER2 (+)

Is there a CT regimen preferred for Her2 + phenotype?

61.4% Yes

36.4% No

2.3% Abstain
Chemotherapy
HER2 (+)

CT regimen should contain:

- Antracyclines: 68 Yes, 22 No, 10 Abstain
- Taxanes: 93.2 Yes, 4.5 No, 2.3 Abstain
Chemotherapy
BASAL-LIKE

Should CT regimen for basal like (triple negative breast cancer – ductal) phenotype contains:

- Antracycline and taxane: 87% Yes, 6.5% No, 6.5% Abstain
- Alkylating agents (not merely AC): 30% Yes, 47.5% No, 22.5% Abstain
- Platinum: 14.6% Yes, 68.8% No, 16.7% Abstain
Should dose dense CT regimen with growth factor support be preferred?

- Yes: 38.3%
- No: 48.9%
- Abstain: 12.8%
Are there reasons other than tumor characteristics to prefer specific CT regimens?

- Yes: 72.7%
- No: 21.2%
- Abstain: 6.1%
Are there reasons other than tumor characteristics to prefer specific CT regimens?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women desiring fertility preservation</td>
<td>76.2</td>
<td>19</td>
<td>4.8</td>
</tr>
<tr>
<td>Avoiding alopecia</td>
<td>56.5</td>
<td>41.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

A. Aydiner
Chemotherapy Preference For Regimen

Are there reasons other than tumor characteristics to prefer specific CT regimens?

Age of patient

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>34</td>
<td>2</td>
</tr>
</tbody>
</table>

Is there any age for not giving chemotherapy?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>37,1</td>
<td>2,9</td>
</tr>
</tbody>
</table>
Are there reasons other than tumor characteristics to prefer specific CT regimens?

Intrinsic subtypes:
- Yes: 37.8%
- No: 53.3%
- Abstain: 8.9%

BRCA carriers:
- Yes: 72.9%
- No: 6.3%
- Abstain: 20.8%
Anti HER-2 Therapy

Minimum T size (invazive diameter) requiring trastuzumab:

- 10 mm
- 5 mm
- Any
Anti HER-2 Therapy

Trastuzumab should be given concurrent with:

- **Taxane:**
  - Yes: 87.2%
  - No: 8.5%
  - Abstain: 4.3%

- **Antracycline:**
  - Yes: 85.7%
  - No: 14.3%
  - Abstain: 0%
Anti HER-2 Therapy

Trastuzumab (+/- endocrine therapy) if CT contraindicated

- ER positive: 75 Yes, 25 No
- ER negative: 85 Yes, 15 No

Legend: 
- Green: Yes
- Red: No
- Yellow: Abstain
Anti HER-2 Therapy

Preferred duration of trastuzumab:

- <1 yr
- 1 yr
- >1 yr

95
5
0
Neoadjuvant Systemic Therapy

Should the only aims of neoadjuvant CT be to facilitate subsequent local therapies?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.9</td>
<td>45.3</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Therapy

After pCR to neoadjuvant CT subsequent adjuvant CT should be given?

- Yes: 95.9%
- No: 0%
- Abstain: 4.1%
**Neoadjuvant Systemic Therapy**

After failure to achieve pCR with neoadjuvant CT, subsequent adjuvant CT should be given?

- Yes: 10
- No: 82.5
- Abstain: 7.5
Neoadjuvant Systemic Therapy

If you are given neoadjuvant CT it is preferred to give entire CT upfront

- Yes: 79.2%
- No: 10.4%
- Abstain: 10.4%
If you have given a less than complete course of chemotherapy and the patient has a pCR, is additional chemotherapy warranted?

- Yes: 62.2%
- No: 26.7%
- Abstain: 11.1%
Neoadjuvant Systemic Therapy
HER2 Positive Disease

Should neoadjuvant systemic therapy contain anti Her2 drugs?

- Yes: 95.9%
- No: 4.1%
- Abstain: 0%
Neoadjuvant Systemic Therapy
HER2 Positive Disease

Should dual HER2-targeting be recommended in the preoperative setting for Her2-positive disease?

- Yes: 37.1
- No: 54.3
- Abstain: 8.6
Neoadjuvant Systemic Therapy: Endocrine Therapy

Is neoadjuvant endocrine therapy alone a reasonable option for postmenopausal patients with high endocrine responsive tumor? (i.e. High ER, low prolif)

- Yes: 93.8%
- No: 2.1%
- Abstain: 4.2%

A. Aydiner
Neoadjuvant Systemic Therapy
Endocrine Therapy

In which duration?

- 3-4 months: 11.1%
- 4-8 months: 26.7%
- Maximal response: 62.2%
### Bisphosphonates

Is zoledronic acid given every 6 months with adjuvant chemotherapy indicated?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Abstain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS improvement for premenopausal women</td>
<td>22.5</td>
<td>70</td>
<td>7.5</td>
</tr>
<tr>
<td>Premenopausal woman requiring LHRHA + TAM</td>
<td>32.6</td>
<td>58.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Premenopausal woman not requiring LHRHA</td>
<td>6.7</td>
<td>6.6</td>
<td>61.7</td>
</tr>
<tr>
<td>Postmenopausal woman</td>
<td>34</td>
<td>61.7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

- Yes
- No
- Abstain
Bisphosphonates

Should adjuvant denosumab substitute for zoledronic acid?

- Yes: 84.4%
- No: 2.2%
- Abstain: 13.3%
Conference Topic

A. Aydiner

Follow-up
Follow-up After Early Breast Cancer

Should all patients have regular follow-up with their surgeon/oncologist (excluding long term endocrine therapy)?

- **Yes**: 70.4%
- **No**: 25.9%
- **Abstain**: 3.7%
Follow-up
After Early Breast Cancer

Is regular follow-up by a nurse specialist or by telephone is an acceptable follow-up?

- By a nurse specialist:
  - Yes: 77.3%
  - No: 15.9%
  - Abstain: 6.8%

- By telephone:
  - Yes: 64.6%
  - No: 22.9%
  - Abstain: 12.5%
Follow-up
After Early Breast Cancer

Should patients have any form of routine imaging apart from mammography as part of their follow-up?

- Yes: 14.9%
- No: 78.7%
- Abstain: 6.4%