GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA
8 Novembre 2014

NEOPLASIA MAMMARIA
Icro Meattini

Radioterapia Oncologica
Azienda Ospedaliero-Universitaria Careggi Firenze
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<th>OVERVIEW</th>
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<tr>
<td>Surgical margins</td>
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<td>Sentinel lymph node(s)</td>
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<tr>
<td>Nodal regions radiotherapy</td>
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<tr>
<td>Partial Breast Irradiation</td>
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<td>Endocrine therapy</td>
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<td>Target therapy</td>
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</tbody>
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OVERVIEW

Surgical margins
Sentinel lymph node(s)
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Partial Breast Irradiation
Endocrine therapy
Target therapy
The SSO/ASTRO guideline concluded that the use of no ink on tumor (ie, no cancer cells adjacent to any inked edge/surface of the specimen) as the standard for an adequate margin in invasive cancer in the era of multidisciplinary therapy is associated with low rates of ipsilateral breast tumor recurrence and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.

Buchholz TA, JCO, 2014
# Final Surgical Margins

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?</td>
<td>A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a two-fold increase in IBTR; this increased risk in IBTR is not nullified by delivery of a boost, delivery of systemic therapy (endocrine, chemotherapy, biologic therapy), or favorable biology.</td>
<td>Meta-analysis, secondary data from prospective trials and retrospective studies</td>
</tr>
<tr>
<td>Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?</td>
<td>Negative margins (no ink on tumor) optimize IBTR; wider margin widths do not significantly lower this risk; the routine practice to obtain wider negative margin widths than ink on tumor is not indicated.</td>
<td>Meta-analysis, retrospective studies</td>
</tr>
<tr>
<td>What are the effects of endocrine or biologically targeted or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?</td>
<td>Rates of IBTR are reduced with the use of systemic therapy; in the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed.</td>
<td>Multiple randomized trials, meta-analysis</td>
</tr>
<tr>
<td>Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)?</td>
<td>Margins wider than no ink on tumor are not indicated based on biologic subtype.</td>
<td>Multiple retrospective studies</td>
</tr>
<tr>
<td>Should margin width be taken into consideration when determining WBRT delivery techniques?</td>
<td>Choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on the margin width.</td>
<td>Retrospective studies</td>
</tr>
<tr>
<td>Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin than no ink on tumor? What is the significance of pleomorphic LCIS at the margin?</td>
<td>Wider negative margins than no ink on tumor are not indicated for invasive lobular cancer; classic LCIS at the margin is not an indication for re-excision; significance of pleomorphic LCIS at the margin is uncertain.</td>
<td>Retrospective studies</td>
</tr>
<tr>
<td>Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (&lt; 40 years)?</td>
<td>Young age (≤ 40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features; there is no evidence that increased margin widths nullifies the increased risk of IBTR in young patients.</td>
<td>Secondary data from prospective randomized trials and retrospective studies</td>
</tr>
<tr>
<td>What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?</td>
<td>EIC identifies cases that may have a large residual DCIS burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative.</td>
<td>Retrospective studies</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO, American Society for Radiation Oncology; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; IBTR, ipsilateral breast tumor recurrence; LCIS, lobular carcinoma in situ; SSO, Society of Surgical Oncology; WBRT, whole-breast radiation therapy.
### Final Surgical Margins

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>What is the absolute increase in risk of IBTR BR</td>
<td>A positive margin, defined as ink on invasive cancer or DCIS, WBRT, this boost, therapy.</td>
</tr>
<tr>
<td>Wider margins have wider margin widths?</td>
<td>that margins wider than no ink on tumor are needed</td>
</tr>
<tr>
<td>Do systemic treatment have wider margin widths?</td>
<td></td>
</tr>
<tr>
<td>Is there any association between increased risk of IBTR when margins are negative?</td>
<td></td>
</tr>
<tr>
<td>What is the systemic treatment burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative?</td>
<td></td>
</tr>
</tbody>
</table>

### Positive margins increase IBTR risk
- Wider margins do not lower IBTR risk
- Systemic therapy do not influence IBTR

### Unfavorable biologic subtypes
- WBRT delivery, dose, fractionation techniques
- Histological variants
- Patients age
- Extensive intraductal component

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**Abbreviations:** ASTRO, American Society for Radiation Oncology; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; IBTR, ipsilateral breast tumor recurrence; LCIS, lobular carcinoma in situ; SSO, Society of Surgical Oncology; WBRT, whole-breast radiation therapy.
Final Surgical Margins

Can Differences of 1-2 mm in Margin Width Be Reliably Identified?

What Does a “Negative” Margin Mean?

A negative margin does not imply that there is no residual tumor in the breast.

<table>
<thead>
<tr>
<th>Margin Width</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 cm</td>
<td>41%</td>
</tr>
<tr>
<td>2 cm</td>
<td>20%</td>
</tr>
</tbody>
</table>

Morrow M, ASTRO 2014, San Francisco
Final Surgical Margins

What We Have Been Doing Is Not Working

- Wide variation in re-excision rates based on surgeon and practice characteristics
  Suggests quality problem, not individualization of care
- There are an estimated 26,550 re-excisions for close margins annually
  Unrealistic to believe each will be discussed in a tumor board
- Avoidance of unnecessary re-excision has the potential to save $30 million/yr using Medicare costs

Key Points Regarding the SSO-ASTRO Margins Consensus

- The consensus does NOT say re-excision to obtain a wider margin is always inappropriate
- Emphasizes that rules routinely requiring specific margin widths > no ink on tumor are not evidence based
- Recognizes that multiple factors beyond tumor burden influence LR

Morrow M, ASTRO 2014, San Francisco
Our experience showed that a **margin-directed** policy of RT **boost dose-escalation** seems to **reduce the negative impact of FMS on LR**, but it is **not able to overcome** the unfavorable effect of higher nuclear grade, higher T stage and triple negative subtype.

<table>
<thead>
<tr>
<th>FMS</th>
<th>BOOST DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5 mm</td>
<td>10 Gy</td>
</tr>
<tr>
<td>5 – 2 mm</td>
<td>16 Gy</td>
</tr>
<tr>
<td>&lt; 2 mm</td>
<td>20 Gy</td>
</tr>
</tbody>
</table>
A boost dose of 16 Gy reduced the local recurrence rate from 13.1% to 8.8% at 15 years and from 16.4% to 12.0% at 20 years (HR: 0.65)

This relative reduction is seen in all age groups, the largest absolute benefit (12%) was observed in younger breast cancer patients.

Bartelink H, ESTRO 2014, Vienna
OVERVIEW

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Sentinel lymph node(s)

Recommendations

Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND).

Women with one to two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases).

Women with SLN metastases who will undergo mastectomy should be offered ALND.

Lyman GH, et al, JCO, 2014
Sentinel lymph node(s)

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Rationale

**ACOSOG Z0011 trial**
Non inferiority trial (OS)

Both studies closed early due to failure to meet their accrual target

**IBCSG 23-01 trial**
Non inferiority (DFS)
SN micrometastases
964 patients


Sentinel lymph node(s)

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Results

No apparent negative impact omitting ALND in mortality

**Non-inferiority in DFS (underpowered)**

No significant differences in terms of recurrences

Statistically significant **higher surgical adverse events** in ALND groups


Sentinel lymph node(s)

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Interpretation

In the experts opinion ALND can be avoided in case of BCS, but only when WBI is planned with conventional fractionation

Consider ALND in case of:

- axillary fine-needle aspiration;
- large or bulky metastatic axillary SLNs;
- gross extranodal tumor extension

Patients with T1—2 primary breast cancer and no palpable nodes
2001-2010
4823 patients
34 centers

2402 patients ALND vs 2404 axillary radiotherapy
1425 patients with a positive sentinel node
744 ALND vs 681 axillary radiotherapy
Median follow-up was 6.1 years for the patients with positive sentinel lymph nodes.

Axillary recurrence occurred in four of 744 patients in the ALND group and seven of 681 in the axillary RT group.

5-year axillary recurrence was 0.43% (95% CI 0.00—0.92) after ALND versus 1.19% (0.31—2.08) after axillary RT.

The planned non-inferiority test was underpowered because of the low number of events.

ALND and axillary RT after a positive sentinel node provide excellent and comparable axillary control for patients with T1—2 primary breast cancer and no palpable lymphadenopathy.
AMAROS trial
Is it a practice changing study?

The extremely **low rate** of axillary recurrence in both study arms does not allow to draw any definitive conclusions.

The trial do not take in account all the **very low-risk patients** (probably a not negligible rate) that could reasonably **not undergo any intervention**.

We have to consider the **suboptimal dose** delivered in adjuvant setting in case of presence of **residual** axillary disease, and the technical challenge of **re-irradiation** in case of recurrence in already irradiated patients.

We do need to continue evaluating results of the contemporary **multidisciplinary approach** in breast cancer to evaluate the final outcome, including **survival** and **toxic effects**.

Axillary RT should be a **valid option** in case of no indication to lymphadenectomy, and it will represent **one more tool** in the hand of the oncologist.
Is Axillary Lymph Node Dissection Necessary After Sentinel Lymph Node Biopsy in Patients with Mastectomy and Pathological N1 Breast Cancer?

This is a retrospective study of 214 patients diagnosed with primary invasive breast cancer who were treated by mastectomy and lymph node staging surgery (SLNB or ALND) at the Revlon/UCLA Breast Center between January 2002 and December 2010. Patients with pathological N1 disease were separated by their first nodal surgery into SLNB (subgroups: observation, radiation, and additional ALND with or without radiation) and ALND groups (subgroups: ALND with or without radiation).

After a median follow-up of 43.6 months, the OS and systemic relapse-free survival (RFS) rate of the radiation group and additional ALND group were significantly better than the observation group (p = 0.031 and 0.046, respectively).

Radiation was as effective as ALND in patients with mastectomy and N1 disease for OS and RFS rates, yet radiation after SLNB had fewer side effects than ALND. SLNB followed by radiation could replace ALND in patients with mastectomy and pathological N1 breast cancer identified by SLNB.

FINAL TREND
The published literature seems to follow the STRONGEST DISCIPLINE, NOT the STRONGEST DATA.
OVERVIEW

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Meta-analysis of individual data for 8135 women randomly assigned to treatment groups during 1964–86 in 22 trials of radiotherapy to the chest wall and regional lymph nodes after mastectomy and axillary surgery versus the same surgery but no radiotherapy

Analyses were stratified by trial, individual follow-up year, age at entry, and pathological nodal status

Follow-up lasted 10 years for recurrence and to Jan 1, 2009, for mortality

EBCTCG, Lancet Oncol, 2014
Nodal regions radiotherapy

### Table A: Any first recurrence (years 0-9)

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/women</th>
<th>RT events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated RT</td>
<td>Allocated no RT</td>
<td>Log-rank O-E</td>
</tr>
<tr>
<td>1 positive node</td>
<td>35/145</td>
<td>63/173</td>
<td>-10.6</td>
</tr>
<tr>
<td>2–3 positive nodes</td>
<td>69/178</td>
<td>92/187</td>
<td>-8.5</td>
</tr>
<tr>
<td>Unknown but pN1–3</td>
<td>73/216</td>
<td>107/234</td>
<td>-18.3</td>
</tr>
<tr>
<td>Total</td>
<td>177/539</td>
<td>262/594</td>
<td>-37.5</td>
</tr>
</tbody>
</table>

**Difference between treatment effects in two categories:** $\chi^2=0.8$; $2p=0.1$, NS

### Table B: Breast cancer mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/women</th>
<th>RT deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated RT</td>
<td>Allocated no RT</td>
<td>Log-rank O-E</td>
</tr>
<tr>
<td>1 positive node</td>
<td>46/145</td>
<td>66/173</td>
<td>-57</td>
</tr>
<tr>
<td>2–3 positive nodes</td>
<td>76/178</td>
<td>96/187</td>
<td>-7.0</td>
</tr>
<tr>
<td>Unknown but pN1–3</td>
<td>80/216</td>
<td>111/234</td>
<td>-11.4</td>
</tr>
<tr>
<td>Total</td>
<td>202/539</td>
<td>273/594</td>
<td>-24.1</td>
</tr>
</tbody>
</table>

**Difference between treatment effects in two categories:** $\chi^2=0.0$; $2p=0.1$, NS

EBCTCG, Lancet Oncol, 2014
Radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given.

**Study period:** 1964-1986

**No sentinel lymph node biopsy** procedure used

**Out-of-date** systemic therapies (CMF schedule and tamoxifen)

**Absolute benefits from postmastectomy radiotherapy** today are likely to be smaller than those reported here

EBCTCG, Lancet Oncol, 2014
Overall, postmastectomy radiotherapy improves locoregional disease-free survival, overall disease-free survival, and breast-cancer-specific survival, irrespective of the number of involved lymph nodes and of administration of adjuvant systemic therapy.

We need to continue evaluating results of the contemporary multidisciplinary approach in breast cancer to better understand the complex interaction between respective contributions of systemic and locoregional treatments to the final outcome, including survival and toxic effects.
Nodal regions radiotherapy

The one in four rule from earlier EBCTCG meta-analyses cannot be generalized to all patient groups.

Radiotherapy can increase the rate of deaths not related to breast cancer, mainly by inducing cardiac diseases and secondary cancers.

This outcome lowers the benefit of radiotherapy on breast cancer mortality after longer follow-up.

However, modern radiotherapy techniques allow the non-intended dose to organs at risk to be decreased, while at the same time improving target coverage.

Continued follow-up is needed to understand fully the ultimate influence of radiotherapy on breast-cancer-related mortality and on late toxic effects.

The results of this EBCTCG meta-analysis clearly confirm that postmastectomy radiotherapy should be considered equally for patients with one to three involved axillary lymph nodes as it should be for patients with four or more affected axillary lymph nodes.
EORTC 22922/10925

- EORTC 22922/10925 trial investigated the potential survival benefit and toxicity of elective irradiation of the internal mammary and medial supraclavicular nodes.

- Between 1996 and 2004, 4004 patients from 43 centres participated, of which 55.6% had involved axillary lymph nodes.

- Nearly all node-positive (99.0%) and 66.3% of node-negative patients received adjuvant systemic treatment.

- Initial 3-year report showed no relevant toxicity following regional node irradiation.

EORTC 22922/10925
10-years Results

• Overall survival at 10 years was 82.3% with and 80.7% without radiation therapy to the internal mammary and medial supraclavicular lymph nodes.

• The causes of death were similar except for breast cancer (259 vs. 310).

• DFS and DMFS were greater after lymph node irradiation.

• The rate of lung and skin toxicity was slightly higher in the regionally irradiated group.

• No increase in cardiac events or lethal complications was observed.

Poortmans, et al, Presidential ECC 2013
Poortmans, et al, ESTRO 2014
Struikmans, et al, EBCC 2014
OVERVIEW

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Partial Breast Irradiation

• APBI demonstrated durable and acceptable local control in biological low risk cases (i.e. luminal A case):
  
  **Stage I; ER positive; > 50 years old**

• Outcome from randomized trials are still needed

• Question **not addressed** by trials:
  
  - Optimal **fractionation**
  - **Dose**
  - **Methodology** to minimize variation in cosmetic outcome

White J, ASTRO 2014
Partial Breast Irradiation

Phase 3 Trial Design

ACCELERATED IMRT TO TREAT THE INDEX QUADRANT
30 Gy in 5 fractions (6 Gy/fr in 2 weeks)

versus

STANDARD WHOLE BREAST RADIOTHERAPY
50 Gy + boost 10 Gy in 30 fractions (2 Gy/fr in 6 weeks)

AFTER CONSERVING SURGERY IN HIGHLY SELECTED EARLY BREAST CANCER PATIENTS

Livi L, et al, IJROBP, 2010
Partial Breast Irradiation

**Low rate** of events at 5-year median follow-up

10 locoregional relapses (4 APBI vs 6 WBI arm)

10 Contralateral breast cancer (3 APBI vs 7 WBI)

<table>
<thead>
<tr>
<th>Events</th>
<th>WBI (n:274)</th>
<th>APBI (n:246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral breast recurrence</td>
<td>5 (1.8%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Local relapse</td>
<td>3 (1.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>New ipsilateral breast tumor</td>
<td>2 (0.7%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Locoregional tumor recurrence</td>
<td>6 (2.2%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>7 (2.6%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>4 (1.5%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>9 (3.3%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4 (1.5%)</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

Accepted as oral presentation at San Antonio Breast Cancer Symposium

*L. Livi, et al*

San Antonio, Texas, 8-13 December, 2014
Partial Breast Irradiation

<table>
<thead>
<tr>
<th></th>
<th>WBI (n:274)</th>
<th>APBI (n:246)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Any skin toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>93</td>
<td>33.9</td>
<td>197</td>
</tr>
<tr>
<td>Yes, any Grade</td>
<td>181</td>
<td>66.1</td>
<td>49</td>
</tr>
<tr>
<td>Grade 1</td>
<td>93</td>
<td>33.9</td>
<td>197</td>
</tr>
<tr>
<td>Grade 2</td>
<td>77</td>
<td>28.1</td>
<td>44</td>
</tr>
<tr>
<td>Grade 3</td>
<td>85</td>
<td>31.1</td>
<td>5</td>
</tr>
<tr>
<td>Grade 4</td>
<td>19</td>
<td>6.9</td>
<td>0</td>
</tr>
<tr>
<td>Grade 0-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>170</td>
<td>62.0</td>
<td>241</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>93</td>
<td>33.9</td>
<td>197</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>162</td>
<td>59.2</td>
<td>49</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>19</td>
<td>6.9</td>
<td>0</td>
</tr>
<tr>
<td>Grade 0-1</td>
<td>225</td>
<td>82.1</td>
<td>246</td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>44</td>
<td>16.1</td>
<td>0</td>
</tr>
<tr>
<td>Breast edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>225</td>
<td>82.1</td>
<td>246</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>44</td>
<td>16.1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>5</td>
<td>1.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Meattini I, et al, ESTRO 2014, Vienna
Partial Breast Irradiation

Meattini I, et al, ESTRO 2014, Vienna
Partial Breast Irradiation

<table>
<thead>
<tr>
<th>Cosmetic result</th>
<th>All patients n=520</th>
<th>&gt;12 months FU n=487</th>
<th>&gt;24 months FU n=457</th>
<th>&gt;36 months FU n=407</th>
<th>&gt;48 months FU n=337</th>
</tr>
</thead>
<tbody>
<tr>
<td>APBI</td>
<td>WBI</td>
<td>APBI</td>
<td>WBI</td>
<td>APBI</td>
<td>WBI</td>
</tr>
<tr>
<td>Excellent</td>
<td>234 (95.1)</td>
<td>247 (90.1)</td>
<td>209 (94.6)</td>
<td>239 (89.8)</td>
<td>186 (93.9)</td>
</tr>
<tr>
<td>Good</td>
<td>12 (4.9)</td>
<td>25 (9.1)</td>
<td>12 (5.4)</td>
<td>25 (9.4)</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Fair</td>
<td>0</td>
<td>2 (0.8)</td>
<td>0</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

-337 patients (64.8%) had a cosmetic evaluation with a minimum follow-up of 48 months

-In both treatment groups the cosmetic result was rated as excellent/good for more than 90% of patients

Meattini I, et al, ESTRO 2014, Vienna
Partial Breast Irradiation

Liss AL, et al, IJROBP, 2014
Partial Breast Irradiation

- The **hypofractionated schedule** commonly used for external beam APBI and prescribed by the ongoing phase 3 trials may be suboptimal.

- **3.85 Gy bid in 5 days** could be a too high dose.

- The **V50 and V100** of the breast reference volume seem correlated with cosmetic outcome.

- **Stricter limits** may be appropriate in this setting.

Liss AL, et al, IJROBP, 2014
Olivotto IA, et al, JCO, 2013
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**Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen, in postmenopausal women with hormone-receptor–positive breast cancer.**

In two phase 3 trials, we randomly assigned premenopausal women with hormone receptor–positive early breast cancer to the aromatase inhibitor exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.

The primary analysis combined data from **4690 patients** in the two trials.

RESULTS

- Median follow-up of 68 months

- Disease-free survival at 5 years was 91.1% in the exemestane–ovarian suppression group and 87.3% in the tamoxifen–ovarian suppression group (HR, 0.72; 95% CI, 0.60 to 0.85; P<0.001).

- Rate of freedom from breast cancer at 5 years was 92.8% in the exemestane–ovarian suppression group, as compared with 88.8% in the tamoxifen–ovarian suppression group (HR, 0.66; 95% CI, 0.55 to 0.80; P<0.001).

- With 194 deaths (4.1%), overall survival did not differ significantly between the two groups (HR, 1.14; 95% CI, 0.86 to 1.51; P=0.37).

- Adverse events of grade 3-4 were 30.6% for the exemestane–ovarian suppression group and 29.4% for the tamoxifen–ovarian suppression group, with profiles similar to those for postmenopausal women.

CONCLUSIONS

In premenopausal women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence.

Premenopausal women who receive ovarian suppression may now benefit from an aromatase inhibitor, a class of drugs that until now has been recommended only for postmenopausal women.

TEXT and SOFT ClinicalTrials.gov numbers, NCT00066703 and NCT00066690

Clifford Hudis, MD, chief of the breast cancer medicine service at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City.

Should premenopausal women with hormone-positive breast cancer have their ovaries shut off as part of treatment, and if they are shut off, do patients do better when an aromatase inhibitor is substituted for tamoxifen?

Joint analysis answers the question, with aromatase inhibitors performing better than tamoxifen.

“What is unanswered here, and this is important, is whether the people who got tamoxifen alone [without OFS] might have done just as well. But for the moment, there is a benefit seen with the aromatase inhibitor therapy, only in terms of disease control.”

For some people, such as those with high-risk disease, “the extra toxicity from being made menopausal will feel worth it,” Hudis said. “Others will say, ‘Without a difference in survival right now, I’m not sure I want to go through this.’”
OVERVIEW

Surgical margins
Sentinel lymph node(s)
Nodal regions radiotherapy
Partial Breast Irradiation
Endocrine therapy
Target therapy
Final overall survival analysis from the CLEOPATRA study of first-line pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer

Sandra M. Swain, Sung-Bae Kim, Javier Cortés, Jungsil Ro, Vladimir Semiglazov, Mario Campone, Eva Ciruelos, Jean-Marc Ferrero, Andreas Schneeweiss, Sarah Heeson, Emma Clark, Graham Ross, Mark C. Benyunes, and José Baselga
CLEOPATRA Study Design

HER2-positive MBC centrally confirmed (N = 808)

1:1

n = 406

Placebo + trastuzumab

PD

n = 402

Docetaxel*

≥ 6 cycles

Pertuzumab + trastuzumab

PD

Docetaxel*

≥ 6 cycles

• Randomization stratified by geographic region and neo/adjuvant chemotherapy

• Study dosing q3w:
  – Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
  – Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
  – Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.
HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease.

Efficacy Analysis Milestones

- **Δ 6.1 months**
- **HR 0.62 (p < 0.0001)**

May 2011

**PFS primary analysis**

HR, hazard ratio.

Efficacy Analysis Milestones

- **PFS primary analysis**
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)

- **OS 1st interim analysis**
  - HR 0.64 (p = 0.005)

May 2011

Efficacy Analysis Milestones

PFS primary analysis

Δ 6.1 months
HR 0.62 (p < 0.0001)

May 2011

May 2012

OS 1st interim analysis

HR 0.64 (p = 0.005)

OS 2nd interim analysis

HR 0.66 (p = 0.0008)*

* Crossed the prespecified O'Brien-Fleming stopping boundary (HR ≤ 0.739; p ≤ 0.0138)

Efficacy Analysis Milestones

May 2011

- PFS primary analysis
- HR 0.64 (p = 0.005)

May 2012

- Δ 6.1 months
- HR 0.62 (p < 0.0001)
- OS 1st interim analysis
- HR 0.66 (p = 0.0008)*

July 2012

- OS 2nd interim analysis
- Patients still on placebo offered crossover to pertuzumab

Efficacy Analysis Milestones

May 2011
- PFS primary analysis
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- OS 2nd interim analysis
- HR 0.66 (p = 0.0008)*

July 2012
- Patients still on placebo offered crossover to pertuzumab

Feb 2014
- OS final analysis

Swain SM, et al. ESMO 2014
Final OS Analysis

Median follow-up 50 months (range 0–70 months)

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

n at risk

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ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain SM, et al. ESMO 2014
Final OS Analysis

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Swain SM, et al. ESMO 2014

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.
Updated PFS
Investigator-Assessed

Ptz + T + D: median 18.7 months
Pla + T + D: median 12.4 months
Δ 6.3 months

HR 0.68
95% CI = 0.58, 0.80
p < 0.0001

Swain SM, et al. ESMO 2014
CLEOPATRA Conclusions

- The addition of pertuzumab to standard 1L therapy significantly improved median OS by **15.7 months**
  - Benefit consistent across subgroups
- Investigator-assessed PFS benefit maintained
- No new safety concerns
  - Long-term cardiac safety maintained

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC

Swain SM, et al. ESMO 2014
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8 Novembre 2014

NEOPLASIA MAMMARIA
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