Surgery for Stage IV Breast Cancer: 

No Benefit at All?

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1. Current status of stage IV breast cancer treatment

Stage IV breast cancer can be any size and has spread to distant sites in the body, usually the bones (70%)\(^1\), lungs (30%)\(^2\) or liver (20%)\(^2\), or brain (10%)\(^3\).

1. Current status of stage IV breast cancer treatment

Treatment status

- About **10–25%** of breast cancer patients present with distant metastases at initial presentation in most Asian countries.
- Cure is not possible for metastatic breast cancers.
- The aim of treatment is to ‘prolong survival and palliate symptoms’.
- Recommended approaches for metastatic breast cancer were **systemic therapy**, which included chemotherapy, endocrine therapy, and targeted drugs.
- Currently, **resection of a primary tumor is not actively recommended by guidelines** due to lack of high-level evidence indicating prognostic benefit.
- Traditionally, surgery has been used only for alleviating chest symptoms, such as bleeding and ulceration as well as pain due to invasion of the chest wall.
1. Current status of stage IV breast cancer treatment

**Stage IV BC – Loco-regional treatment?**

- **Conventional:**
  - Systemic treatment
  - Surgery of the primary site: ‘palliation’ or ‘symptom control’:
    - Ulceration
    - Infection
    - Bleeding
    - Quality of life

- **Challenge:**
  - Which patients could benefit from surgery of the primary tumor?
  - Timing of the surgery?
  - Intend of the surgery?
  - Possible benefit to be expected?
2. Retrospective data on locoregional surgery

Theoretical explanations of the effect of surgery

• A reduction in circulating tumor cells (CTCs) according to primary tumor resection reportedly correlates with prognosis

• Resection of the primary tumor can reduce the tumor volume, including that of cancer stem cells, thereby reactivating autoimmunity and increasing the efficacy of systemic therapies

• Reducing cancer cells released into the blood from the primary tumor

Until now, retrospective studies regarding surgery in patients with primary metastatic breast cancer have found that surgical removal of the breast lesion is associated with a significantly higher overall survival rate. 

*Eur J Cancer. 2011 Sep;47 Suppl 3:S6-22.*
2. Retrospective data on locoregional surgery

Surgery of primary tumors in stage IV breast cancer: an updated analysis of published studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>[V, Random, 95% CI]</th>
<th>[V, Random, 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babiera 2005</td>
<td>-0.69</td>
<td>0.44</td>
<td>1.3%</td>
<td>0.50 [0.21, 1.19]</td>
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</tr>
<tr>
<td>Bafford 2008</td>
<td>-0.75</td>
<td>0.25</td>
<td>3.5%</td>
<td>0.47 [0.29, 0.77]</td>
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<tr>
<td>Blanchard 2007</td>
<td>-0.34</td>
<td>0.12</td>
<td>9.4%</td>
<td>0.71 [0.56, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Cady 2008</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Fields 2007</td>
<td>-0.63</td>
<td>0.119</td>
<td>9.8%</td>
<td>0.53 [0.42, 0.67]</td>
<td></td>
</tr>
<tr>
<td>Gneifich 2007</td>
<td>-0.48</td>
<td>0.029</td>
<td>19.0%</td>
<td>0.82 [0.58, 0.65]</td>
<td></td>
</tr>
<tr>
<td>Khan 2002 (1)</td>
<td>-0.49</td>
<td>0.029</td>
<td>19.0%</td>
<td>0.61 [0.58, 0.65]</td>
<td></td>
</tr>
<tr>
<td>Khan 2002 (2)</td>
<td>-0.29</td>
<td>0.027</td>
<td>19.1%</td>
<td>0.75 [0.71, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Leung 2009</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Rapiti 2006 (1)</td>
<td>-0.51</td>
<td>0.234</td>
<td>3.9%</td>
<td>0.60 [0.38, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Rapiti 2006 (2)</td>
<td>0.26</td>
<td>0.246</td>
<td>3.6%</td>
<td>1.30 [0.80, 2.10]</td>
<td></td>
</tr>
<tr>
<td>Rütterkamp 2009</td>
<td>-0.48</td>
<td>0.102</td>
<td>11.3%</td>
<td>0.62 [0.51, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td></td>
<td>0.65 [0.59, 0.72]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.01; \chi^2 = 47.04, df = 9 (P < 0.00001); I^2 = 81\%$
Test for overall effect: $Z = 8.38 (P < 0.00001)$

The HR for overall mortality varied from 0.47 to 0.71 and pooled HR was 0.65 (95% confidence interval [CI] 0.59–0.72) in favour of patients undergoing surgery.

2. Retrospective data on locoregional surgery

U.S. cohort study

Original Investigation


• A retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) program.

• Stage IV breast cancer female patients between 1988 and 2011 and who did not receive radiation therapy as part of the first course of treatment were included (N = 21372).

• Endpoints: Differences in survival, particularly survival of at least 10 years

2. Retrospective data on locoregional surgery

U.S. cohort study

Median survival in months and estimated by receipt surgery

"For the entire cohort, the median survival was 23 months."

"The surgical patients had longer median survival than those who did not (28 months vs 19 months; 95% CI, 7.6-10.4)."

"Women with tumors 2 cm or smaller had an additional improvement in survival of 11 months (95% CI, 6.4-15.6) with surgery."

2. Retrospective data on locoregional surgery

U.S. cohort study

Estimates from the survival model reveal an association between surgery and longer survival.

<table>
<thead>
<tr>
<th>Table 3. HRs for Women With Stage IV Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Local therapy</strong></td>
</tr>
<tr>
<td>No surgery</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td><strong>Age at diagnosis, y</strong></td>
</tr>
<tr>
<td>&lt;45</td>
</tr>
<tr>
<td>45–64</td>
</tr>
<tr>
<td>≥65</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
</tr>
<tr>
<td>≤2 cm</td>
</tr>
<tr>
<td>&gt;2–5 cm</td>
</tr>
<tr>
<td>&gt;5 cm</td>
</tr>
</tbody>
</table>

Receipt of surgery (hazard ratio, 0.60; 95% CI, 0.57-0.63) was associated with longer survival.

2. Retrospective data on locoregional surgery

U.S. cohort study

On multivariate analysis, survival of at least 10 years was most strongly associated with surgery.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Surgery</td>
<td><strong>2.80 (2.08-3.77)</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>0.97 (0.69-1.35)</td>
<td>.85</td>
</tr>
<tr>
<td>45-64</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>≥65</td>
<td>0.41 (0.32-0.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;2-5 cm</td>
<td>0.76 (0.58-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>0.37 (0.27-0.51)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Patients who received surgery were **2.80 times** more likely to survive at least 10 years than those who did not (95% CI, 2.08-3.77).

2. Retrospective data on locoregional surgery

Results-U.S. cohort study

- Receipt of surgery was associated with improved survival in multivariate analysis, along with time period (HR 0.60; 95%CI, 0.57-0.63).

- For women diagnosed as having cancer before 2002 (n = 7504), survival of at least 10 years was 9.6%(n = 353) and 2.9% (n = 107) of those who did and did not receive surgery, respectively (OR, 3.61; 95%CI, 2.89-4.50).

- Survival of at least 10 years was associated with receipt of surgery (odds ratio, 2.80; 95%CI, 2.08-3.77).

- Survival in stage IV breast cancer has improved and is increasingly of prolonged duration, particularly for some women undergoing initial breast surgery.

2. Retrospective data on locoregional surgery

ALN resection study

Therapeutic role of axillary lymph node dissection in patients with stage IV breast cancer: a population-based analysis

- **Purpose:** To assess the clinical value of axillary lymph node (ALN) dissection in stage IV breast cancer.
- Patients with a diagnosis of stage IV breast cancer from 1990 to 2010 were identified using SEER database.
- A total of 11,645 patients were identified. Of these, 7358 (63.2%) patients underwent ALN dissection, and 6168 (83.8%) patients showed nodal positivity.
- Patients with delayed diagnosis, age <50 years, poorly/undifferentiated disease, larger tumor size (>2 cm), and married women were more likely to undergo ALN dissection.

2. Retrospective data on locoregional surgery

ALN resection study

Impact of lymph node dissection on breast cancer-specific survival (A) and overall survival (B) in stage IV breast cancer

(A) The 5-year BCSS was 40.2 and 24.2% and the median BCSS was 43 and 25 months in ALN dissection group and non-ALN dissection group, respectively (log-rank test, p < 0.001).

(B) The 5-year OS was 35.0 and 19.1% and the median OS time was 38 versus 21 months in the ALN dissection group and non-ALN dissection group, respectively, (log-rank test, p < 0.001).

2. Retrospective data on locoregional surgery

ALN resection study

Impact of lymph node staging on breast cancer-specific survival (A) and overall survival (B) in stage IV breast cancer

(A) The 5-year BCSS was 56.4, 44.4, 36.4, and 29.7% in patients with N0, N1, N2, and N3 staging, respectively. The median BCSS was 78, 48, 39, and 34 months, respectively (p < 0.001).

(B) The 5-year OS was 48.9, 38.5, 32.1, and 25.6% in patients with N0, N1, N2, and N3 staging, respectively. The median OS was 57, 41, 36, and 30 months, respectively (p < 0.001).

Results – ALN resection study

- ALN dissection was associated with improved BCSS and OS.

- ALN dissection may improve survival in patients with stage IV breast cancer who received primary tumor surgery, especially in patients with bone, liver, and single site of distant metastasis.

- The lymph node staging was also the prognostic factor in patients with stage IV breast cancer.

2. Retrospective data on locoregional surgery

A single center retrospective study from Tianjin

A comparative analysis of surgical treatment to primary tumor in patients with metastatic breast cancer.

• 120 metastatic breast cancer patients from January 2005 to December 2012 were collected.

• All cases were divided into surgical and nonsurgical groups, and the overall survival and symptomatic local progression rates were analyzed.

• The patients had a median follow-up of 52 months (range=10-92 months).

• A total of 55 cases were in the surgical group, 30 of whom had surgery before the metastatic diagnosis, and 65 cases were in the nonsurgical group.

*Chin Clin Oncol 2014;6(1):45-8*
2. Retrospective data on locoregional surgery

**Results-Tianjin study**

- Patients in the surgical group experienced longer overall survival (49 months vs. 33 months, P=0.016, Fig. A) and local progression-free survival time (38 months vs. 16 months, P=0.0001, Fig. B).
- The study demonstrated that the overall survival and symptomatic local control in the surgical group were better than those in the nonsurgical group.

*Chin Clin Oncol 2014;6(1):45-8*
2. Retrospective data on locoregional surgery

Brief Summary

Potential Benefit for surgery

- Surgery of the primary tumor was independently associated with longer survival (hazard ratio [HR], 0.69; P<.00001)*.
- The survival benefit was independent of age, tumor burden, type of surgery, margin status, site of metastases, hormone receptor status, and HER2 status.
- Use of systemic therapy and radiotherapy were significantly associated with survival.

*J Natl Compr Canc Netw. 2015 Apr;13(4):487-93
Potential Biases

Surgical Timing

The timing of surgery in relation to the diagnosis of metastases and use of systemic therapy has not always been specified in the published retrospective literature. This is a source of bias in that women who are diagnosed with metastases only after they have undergone surgery for the primary tumor most likely have asymptomatic (and therefore lower-volume) metastases.

Other sources of bias

Women who received surgery tended to be younger, have smaller tumors, have fewer comorbidities, have a lower burden of metastatic disease, be less likely to have visceral metastases, and be likely to have better access to care.

*J Natl Compr Canc Netw. 2015 Apr;13(4):487-93*
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Randomized Clinical Trials of Surgery on Stage IV breast cancer

<table>
<thead>
<tr>
<th>Country</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Accrual Period</th>
<th>N</th>
<th>Initial Therapy</th>
<th>Radiotherapy</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>NCT00193778a</td>
<td>2005-2012</td>
<td>350</td>
<td>Adriamycin, cyclophosphamide, 5-FU</td>
<td>If indicated</td>
<td>Time to progression</td>
</tr>
<tr>
<td>Japan</td>
<td>JCOG1017b</td>
<td>2011-2016</td>
<td>410</td>
<td>Systemic therapy</td>
<td>Not addressed</td>
<td>Survival</td>
</tr>
<tr>
<td>USA and Canada</td>
<td>NCT01242800c</td>
<td>2011-2016</td>
<td>368</td>
<td>Systemic therapy</td>
<td>Per standards for stage I-III</td>
<td>Survival</td>
</tr>
<tr>
<td>Turkey</td>
<td>NCT00557986d</td>
<td>2008-2012</td>
<td>281</td>
<td>Surgery</td>
<td>For breast conservation</td>
<td>Survival</td>
</tr>
<tr>
<td>Thailand</td>
<td>NCT01906112e</td>
<td>2013-2019</td>
<td>476</td>
<td>Surgery</td>
<td>Not addressed</td>
<td>Survival</td>
</tr>
<tr>
<td>Austria</td>
<td>NCT01015625f</td>
<td>2010-2019</td>
<td>254</td>
<td>Surgery</td>
<td>Per standards for stage I-III</td>
<td>Survival</td>
</tr>
</tbody>
</table>

*Assessing Impact of Locoregional Treatment on Survival in Metastatic Breast Cancer at Presentation.
*bA Randomized Controlled Trial Comparing Primary Tumor Resection Plus Systemic Therapy With Systemic Therapy Alone in Metastatic Breast Cancer.
*cEarly Surgery or Standard Palliative Therapy in Treating Patients With Stage IV Breast Cancer.
*dLocal Surgery for Metastatic Breast Cancer.
*eRole of Surgery for the Primary in Patients With Breast Cancer Stage IV.
*fPrimary Operation in Synchronous Metastasized Invasive Breast Cancer (POSITIVE).

3. Prospective trial evaluating locoregional surgery

Three Studies completed with different Design and Results.

Trials Requiring Induction Systemic Therapy

-- Indian trial¹ (NCT00193778)

-- U.S. trial² (NCT00941759)

Trials Requiring Randomization to Surgery Before Systemic Therapy

-- Turkish trial³ (NCT00557986)

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomized controlled trial (ClinicalTrials.gov, NCT00193778).

- Locoregional treatment consisted of a standard surgical procedure that was either mastectomy or breast conserving surgery accompanied by full axillary lymph node dissection.
- Patients (≤65 years of age with an estimated remaining life expectancy of at least 1 year) presenting with de-novo metastatic breast were recruited.
- 173 patients were randomly assigned to receive locoregional treatment directed at their primary breast tumour and axillary lymph nodes and 177 patients were assigned to receive no locoregional treatment.
- Induction therapy consisted of anthracyclines with or without taxanes, or endocrine therapy.

Locoregional treatment did not result in a significant improvement in overall survival compared with no locoregional treatment (median survival 19.2 months [95% CI 15.98–22.46] vs 20.5 months [16.96–23.98]; HR 1.04, 95% CI 0.81–1.34; p=0.79.

(A). Locoregional treatment resulted in a significant improvement in progression-free survival compared with that in the no locoregional treatment group (median not attained vs 18.2 months [95% CI 15.1–21.3]; HR 0.16, 95% CI 0.10–0.26; p<0.0001).

(B). Locoregional treatment resulted in a significant detriment in distant progression-free survival compared with that in the no locoregional treatment group (median 11.3 months [95% CI 7.7–14.8] vs 19.8 months [10.26–29.0]; HR 1.42, 95% CI 1.08–1.85; p=0.012).

3. Prospective trial evaluating locoregional surgery

Results - Indian trial

• **Median overall survival** was **19.2 months** (95% CI 15.98–22.46) in the locoregional treatment group and **20.5 months** (16.96–23.98) in the no-locoregional treatment group (HR 1.04, 95% CI 0.81–1.34; p=0.79).

• **Local progression-free survival** was significantly better in the surgical group (80% at 5 years v.s 20% in the nonsurgical group; **P<0.001**).

• **No significant differences in survival** were seen in subset analyses (menopausal status, visceral vs bone metastases, >3 vs 1–3 metastatic sites, and hormone receptor/HER2 status).

• **There is no evidence to suggest that locoregional treatment** of the primary tumor affects overall survival in patients with metastatic breast cancer at initial presentation who have responded to front-line chemotherapy, and this procedure should not be part of routine practice.

3. Prospective trial evaluating locoregional surgery

**U.S. Study (TBCRC 013)—2016 ASCO**

A prospective analysis of surgery and survival in stage IV breast cancer.

- A multicenter prospective registry study evaluating the role of surgery for the primary tumor in de novo Stage IV disease.
- 127 pts from were enrolled in 2 cohorts (A: Stage IV with intact primary (n = 112); B: metastases within 3 mos of primary surgery (n = 15)). All patients received 1st-line systemic therapy per treating physician.
- In Cohort A, patients classified as responders to 1st-line therapy (partial, complete, or stable distant disease) were referred to discuss surgery.
- Among 112 pts in Cohort A, 94 (85%) patients were classified as responders; 3 yr OS responders vs. non-responders, 78% (95%CI,70-87) vs 24% (95%CI,10-55), p < 0.001.
- Among responders, 39 (41%) chose surgery with no impact on 3y OS (77% with vs 76% without surgery).

3. Prospective trial evaluating locoregional surgery

U.S. Study (TBCRC 013)—2016 ASCO

Among responders, surgery did not impact OS irrespective of tumor subtype.

<table>
<thead>
<tr>
<th>Responders</th>
<th>Surgery</th>
<th>N</th>
<th>Median Survival, mos (95%CI)</th>
<th>3yr OS (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>N</td>
<td>51</td>
<td>71 (56-NR)</td>
<td>75 (66-89)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>39</td>
<td>77 (52-NR)</td>
<td>77 (65-91)</td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>N</td>
<td>46</td>
<td>71 (56-NR)</td>
<td>78 (67–91)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>34</td>
<td>77 (53-NR)</td>
<td>79 (67-94)</td>
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<tr>
<td>HER2+</td>
<td>N</td>
<td>12</td>
<td>NR (NR-NR)</td>
<td>83 (65-100)</td>
<td>0.39</td>
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<tr>
<td></td>
<td>Y</td>
<td>15</td>
<td>77 (77-NR)</td>
<td>100 (100-100)</td>
<td></td>
</tr>
</tbody>
</table>

3. Prospective trial evaluating locoregional surgery

Results- U.S. Study (TBCRC 013)

• Patients who chose surgery had larger tumors (3.8cm vs 3.2cm, p = 0.01), were more likely to have single organ metastatic disease (77% vs 41%, p = 0.001) and to have received 1st-line chemotherapy (39% vs 17%, p = 0.002).

• Among responders, surgery was not associated with improved survival for any subtype (ER+HER2-, p = 0.37; ER+HER2+, p = 0.07; ER-HER2+, p = 0.51; ER-HER2-, sample too small).

Turkish study (protocol MF07-01)--2016 ASCO

A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer.

- A multicenter phase III randomized trial of treatment stage IV BC patients comparing loco-regional surgery (LRS) followed by appropriate systemic therapy (ST) vs ST alone.
- Aims: To compare 3-year survival and loco-regional progression (LRP).
- At initial diagnosis patients were randomized 1:1 to LRS group or ST group, 274 patients were accrued; 138 in the LRS group and 136 in the ST group.
- Patients with positive nodes received axillary clearance, and hormonal therapy and/or trastuzumab (Herceptin) was given if indicated.
- There were 76 (55%) deaths in the LRS group and 101 (74%) in the ST group during the median 40 (20-51) months follow-up.

3. Prospective trial evaluating locoregional surgery

Turkish study (protocol MF07-01)--2016 ASCO

Table 1: Post Hoc Subgroup Analysis of 5-Year Overall Survival (N = 274)

<table>
<thead>
<tr>
<th>Subset</th>
<th>Surgery</th>
<th>Systemic Treatment</th>
<th>HR; P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR-positive</td>
<td>46.4%</td>
<td>26.4%</td>
<td>HR = 0.64; P = .011</td>
</tr>
<tr>
<td>HER2-negative</td>
<td>41.9%</td>
<td>23.1%</td>
<td>HR = 0.64; P = .012</td>
</tr>
<tr>
<td>Age &lt; 55 years</td>
<td>46.9%</td>
<td>24.0%</td>
<td>HR = 0.57; P = .01</td>
</tr>
<tr>
<td>Multiple pulmonary/liver metastases</td>
<td>31.0%</td>
<td>67.0%</td>
<td>HR = 1.49; P = .39</td>
</tr>
<tr>
<td>Solitary bone metastasis</td>
<td>51.7%</td>
<td>29.2%</td>
<td>HR = 0.47; P = .038</td>
</tr>
<tr>
<td>Bone-only metastasis</td>
<td>45.1%</td>
<td>31.1%</td>
<td>HR = 0.67; P = .12</td>
</tr>
</tbody>
</table>

HR = hazard ratio; ER/PR = estrogen receptor/progesterone receptor.

ER (+), HER2 (-), solitary bone metastasis, and patients < 55 years old have a significant survival benefit with initial surgery

Results-- Turkish study

- At 36 months, the survival rate was similar the LRS group and the ST group (60% and 51%, respectively; p = 0.5). OS was 34% higher in the LRS group compared to the ST group (HR: 0.66, 95%CI 0.49-0.88; p = 0.005).
- Patients with a more indolent form of metastatic BC such as ER (+), HER2 (-), solitary bone metastasis, and patients < 55 years old have a significant survival benefit with initial surgery.
- The median survival was 14 months higher in the LRS group comparing with the ST group in only bone metastasis (56 vs 42 months; HR 0.67, 95%CI 0.43-1.07; p = 0.09).

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3. Prospective trial evaluating primary tumor resection
4. Retrospective data on metastases resection
Surveillance, Epidemiology, and End Results database (SEER) was used to explore the impact of surgery on the survival of stage IV breast cancer patients.

10,441 eligible stage IV breast cancer patients from 2004 to 2008 were included.

Four groups were divided:
- R0 group (patients who underwent primary site and distant metastatic site resection),
- primary site resection group
- metastases resection group
- no resection group

R0 group showed the best overall survival outcome with a median survival time (MST) of 51 months, followed by the primary resection group (MST = 43 months) and metastases resection group (MST = 31 months). The no resection group achieved an MST of 21 months. The difference among the four groups was significant ($P < 0.001$).

4. Retrospective data on metastases resection

Metastatic sites resection study

**Overall survival curves of the four groups**

![Survival curves](chart.png)

Figure 1: Overall survival curves of the four groups.

In the HR+ population, the survival of each group with surgery, including the R0 resection group (MST = 66 m; 5-year OS = 54.1%), primary resection group (MST = 52 m; 5-year OS = 44.9%) and metastases resection group (MST = 38 m; 5-year OS = 31.7%) were all significantly longer than the no resection group (MST = 28 m; 5-year OS = 22.0%) (P values were all < 0.001).

In the HR-population, the survivals of the R0 group (MST = 18 m; 5-year OS = 26.7%) and primary resection group (MST = 24 m; 5-year OS = 25.0%) were both significantly longer than the no resection group (MST = 12 m; 5-year OS = 11.8%) but not the metastases resection group (MST = 12 m, 5-year OS = 6.8%) \( (P = 0.526) \).
Results-Metastatic sites resection study

- R0 group, primary resection group and metastases resection group had a good survival benefit, with hazard ratios of 0.558 (95% CI, 0.471-0.661), 0.566 (95% CI, 0.557-0.625) and 0.782 (95% CI, 0.693-0.883), respectively.

- In the HR-positive population, the R0 group (MST = 66 m, 5-year OS = 54.1%) gained an additional survival benefit compared with the primary resection group (MST = 52 m; 5-year OS = 44.9%; P < 0.001).

- In the HR-negative population, the R0 group and primary resection group had a similar survival (P = 0.691), and the metastases resection group had a similar outcome to that of the no resection group (P = 0.526).

- Patients who underwent surgery for stage IV breast cancer showed better overall survival than the no resection group. Cytoreductive surgery could provide a survival benefit in HR+ stage IV breast cancer.

Conclusions

• Although the retrospective data and Turkish study (NCT00557986) suggest that locoregional therapy may provide a survival advantage in women with metastatic breast cancer, this is not confirmed by 2 randomized trials (ClinicalTrials.gov identifiers: NCT00193778 [Indian study] and NCT00941759 [U.S. study]).

• The biases of the retrospective studies weaken the reliability of effect of surgery on stage IV breast cancer.

• For the patient whose distant disease is controlled but the primary site is progressing, surgery provides a reasonable approach.

• For some patients, metastatic sites resection combining with primary tumor resection may bring about an additional improvement of survival.
Conclusions

Ongoing trials will allow for the role of surgery alone or surgery plus radiotherapy to be evaluated, and will allow solid conclusions to be reached regarding the role of locoregional therapy, how extensive it should be, and its timing in stage IV breast cancer.

Until additional unbiased data are available, surgery should not be routinely recommended for patients with stage IV breast cancer with an intact primary tumor.
Thank you!