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Surgery for Stage IV Breast Cancer: No Benefit at All?

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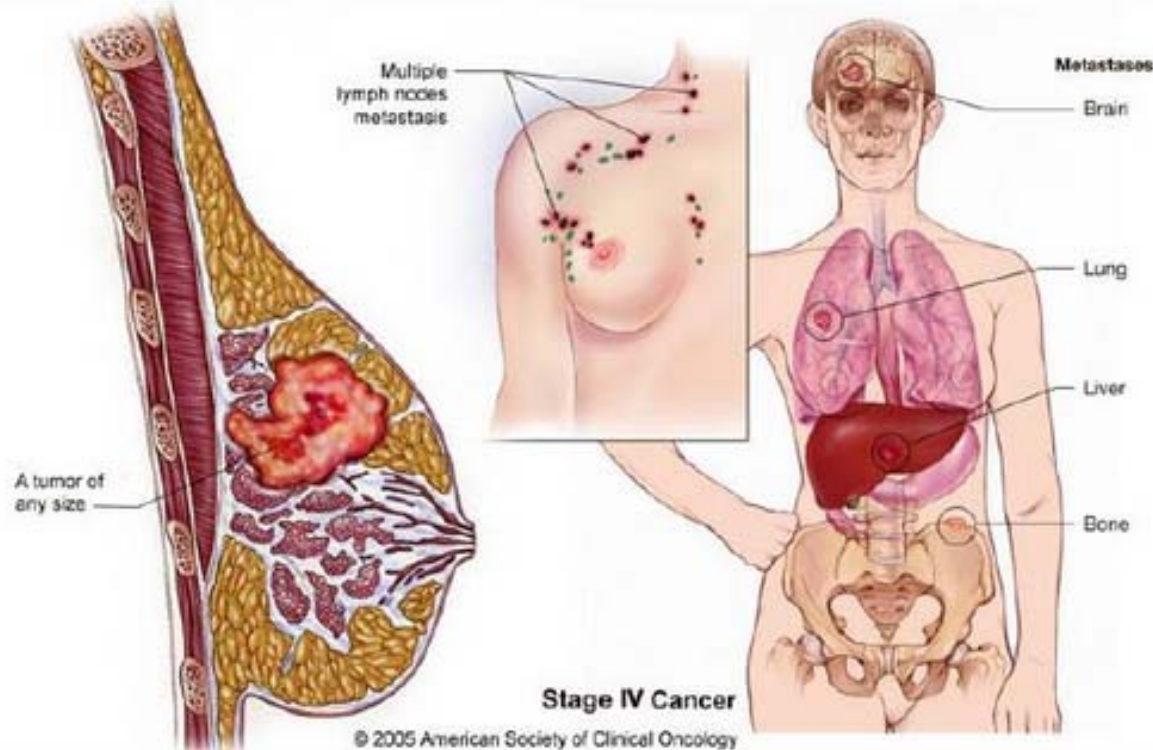
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1. Current status of stage IV breast cancer treatment

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. *Lancet Oncol.* 2009 Jun;10(6):606-14.

2. *J Cancer Res Clin Oncol.* 2017 Mar;143(3):467-474.

3. *Nature.* 2009 Jun 18;459(7249):1005-9.



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?



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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



2. Retrospective data on locoregional surgery

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

Table 1
Results of literature on surgery in patients with primary distant metastatic breast cancer

Author (Year)	No. of patients	Surgery (%)	HR	95% CI	Median survival (months)			
					Surgery		No surgery	
					All	Lumpec		Mastec
Khan (2002) [1]	16023	57	0.61	0.58–0.65	–	27	32	19
Babiera (2006) [2]	224	37	0.50	0.21–1.19	–	–	–	–
Rapiti (2006) [3]	300	42	0.60	0.4–1.0	^a	–	–	–
Fields (2007) [5]	409	46	0.53	0.42–0.67	32	–	–	15
Gnerlich (2007) [4]	9734	47	0.63	0.60–0.66	36	–	–	21
Blanchard (2008) [6]	395	61	0.71	0.56–0.91	27	–	–	17
Cady (2008) [10]	622	38	–	–	–	–	–	–
Leung (2009) [11]	157	33	–	–	25	–	–	13
Ruiterkamp (2009) [7]	728	40	0.62	0.51–0.76	31	–	–	14
Bafford (2009) [12]	147	41	0.47	–	42	–	–	28
Neuman (2010) [8]	186	37	0.71	0.47–1.06	40	–	–	33

HR: Hazard ratio; 95% CI: 95% confidence interval.

^a 5-year specific survival: 27% for surgery with negative margins, 16% for surgery with positive margins, 12% for surgery with unknown margins and 12% for no surgery.

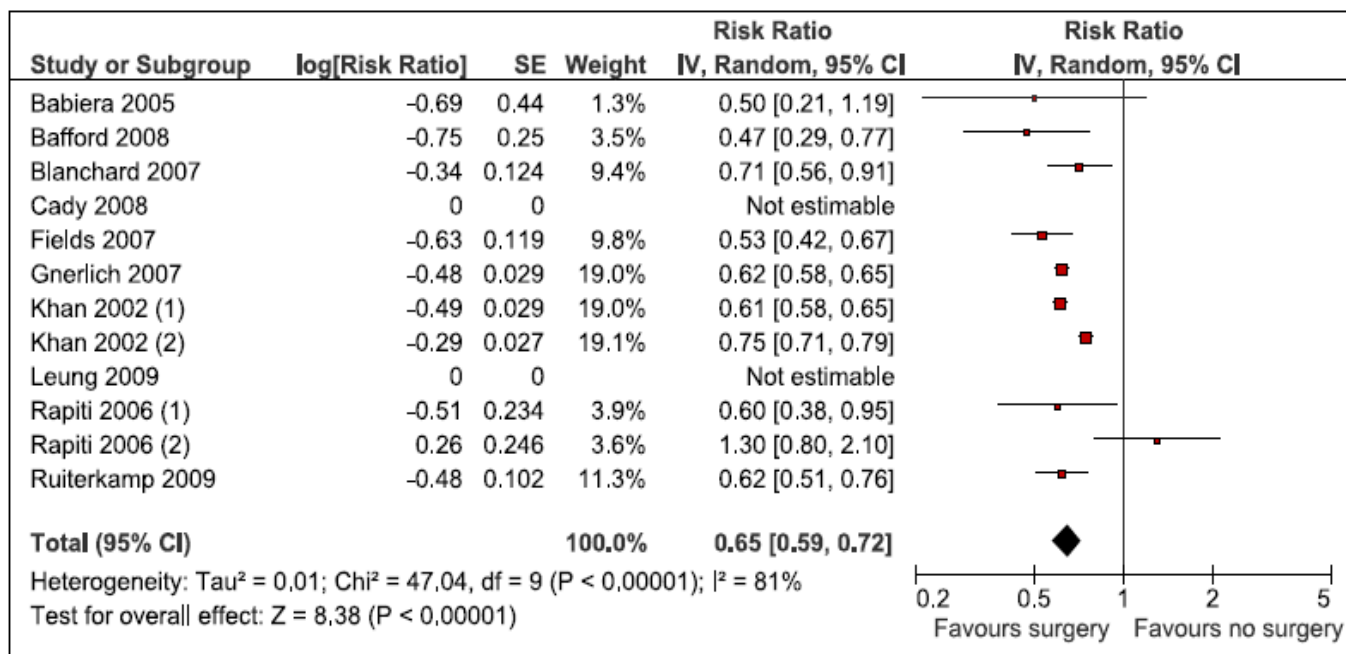
Until now, retrospective studies regarding surgery in patients with primary metastatic breast cancer have found that **surgical removal of the breast lesion is associated with a significantly higher overall survival rate.**

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



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

Initial Surgery and Survival in Stage IV Breast Cancer in the United States, 1988-2011

- 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

Table 2. Median Survival in Months and Estimated HR by Receipt of Surgery

Characteristic	Median Survival, mo			HR (95% CI) ^a
	Full Sample (n = 21 372)	No Surgery (n = 13 042)	Surgery (n = 8330)	
Full sample	23	19	28	0.68 (0.66-0.70)
Age, y				
<45	28	24	34	0.71 (0.63-0.78)
45-64	27	22	35	0.65 (0.62-0.69)
≥65	17	14	23	0.71 (0.68-0.74)
Tumor size				
≤2 cm	27	23	34	0.69 (0.63-0.75)
>2-5 cm	27	21	32	0.67 (0.63-0.71)
>5 cm	20	17	24	0.78 (0.73-0.83)

- For the entire cohort, the median survival was **23** months.
- The surgical patients had longer median survival than those who did not (**28months vs 19months** ;95% CI, 7.6-10.4).
- Women with **tumors 2 cm or smaller** had an additional improvement in survival of **11months** (95%CI, 6.4- 15.6)with surgery.

JAMA Surg. 2016 May 1;151(5):424-31.



2. Retrospective data on locoregional surgery

U.S. cohort study

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

Table 3. HRs for Women With Stage IV Breast Cancer

Characteristic	HR (95% CI) ^a	P Value
Local therapy		
No surgery	1 [Reference]	NA
Surgery	0.60 (0.57-0.63)	<.001
Age at diagnosis, y		
<45	0.77 (0.70-0.85)	<.001
45-64	1 [Reference]	NA
≥65	1.54 (1.46-1.62)	<.001
Tumor size		
≤2 cm	1 [Reference]	NA
>2-5 cm	1.06 (1.00-1.11)	.045
>5 cm	1.25 (1.18-1.31)	<.001

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

JAMA Surg. 2016 May 1;151(5):424-31.



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 4. Multivariate Logistic Model Predicting 10 or More Years of Survival*

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

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).

JAMA Surg. 2016 May 1;151(5):424-31.



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

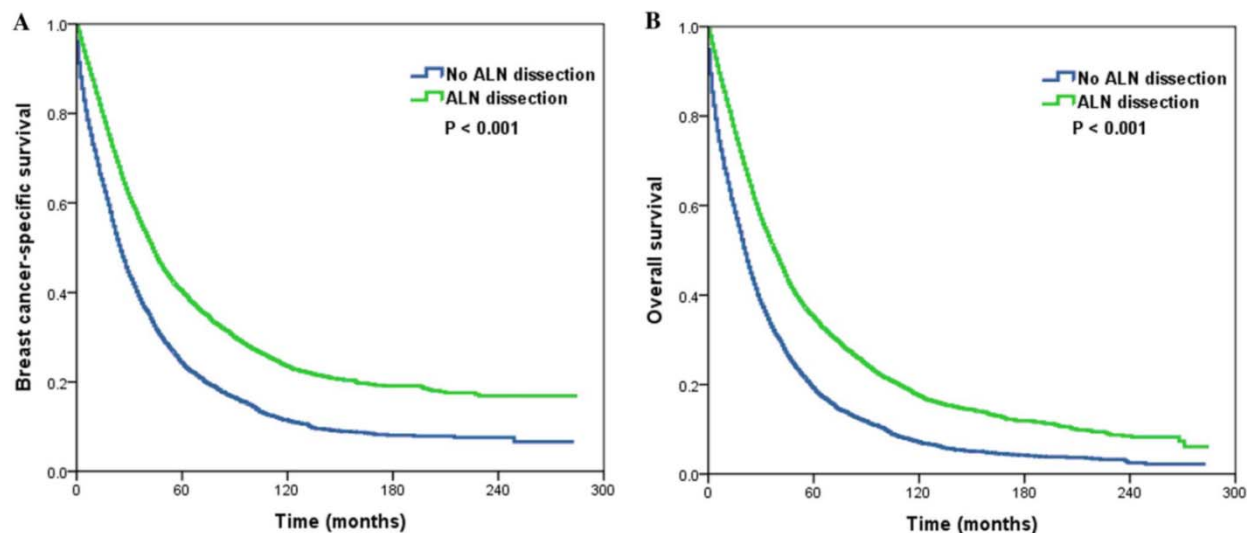
Therapeutic role of axillary lymph node dissection in patients with stage IV breast cancer: a population-based analysis

- **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

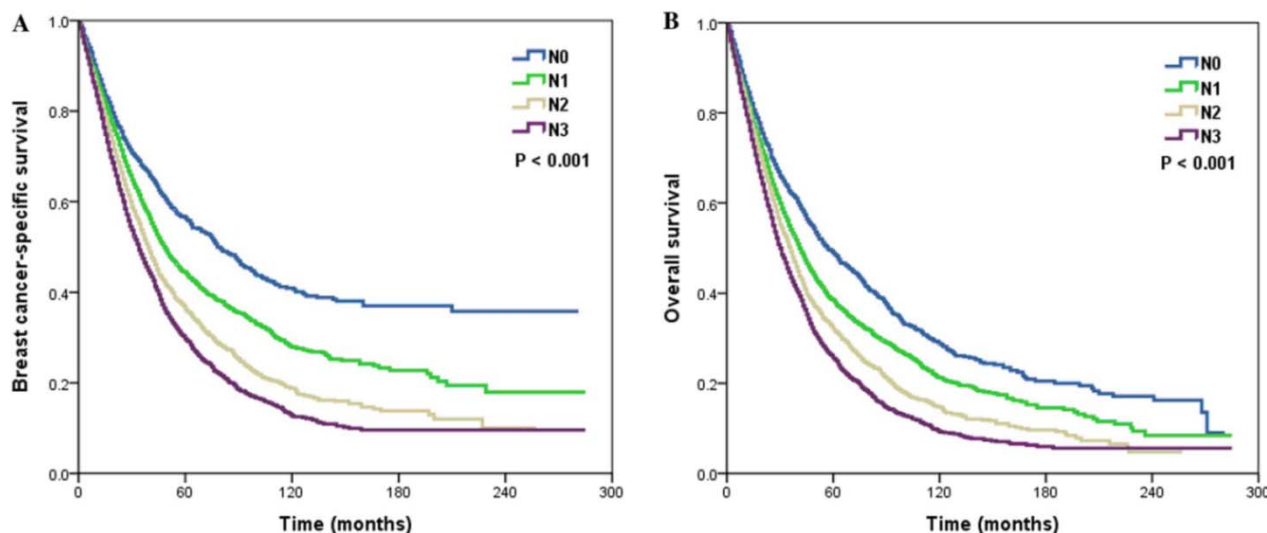


- (A) The 5-year BCSS was 40.2 and 24.2% and the median BCSS was **43 and 25 months in ALN dissection group and non-ALN dissection group**, respectively (log-rank test, $p < 0.001$).
- (B) The 5-year OS was 35.0 and 19.1% and the median OS time was **38 versus 21 months in the ALN dissection group and 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).



2. Retrospective data on locoregional surgery

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**.

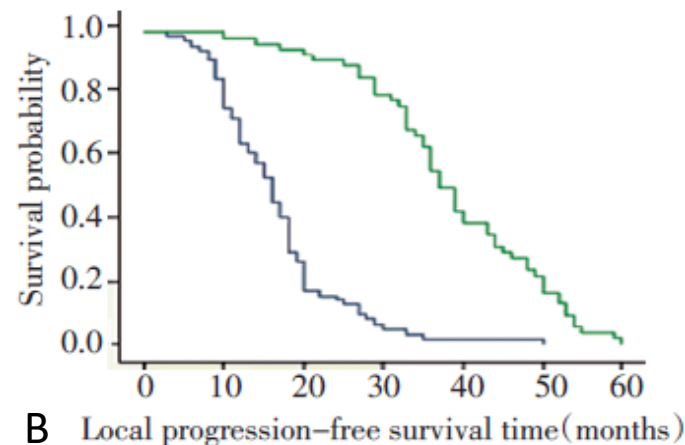
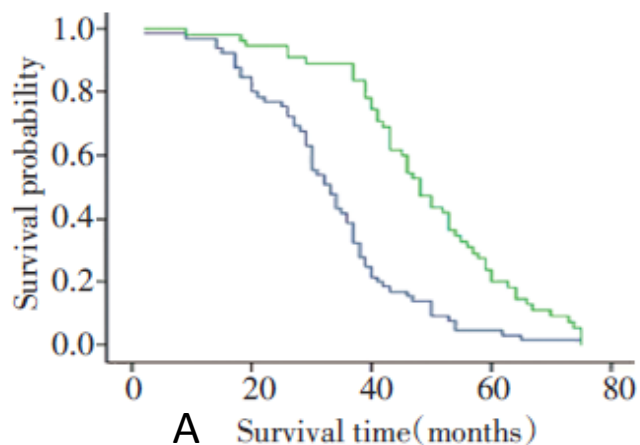


2. Retrospective data on locoregional surgery

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.





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*



2. Retrospective data on locoregional surgery

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.**



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3. Prospective trial evaluating locoregional surgery

Randomized Clinical Trials of Surgery on Stage IV breast cancer

Table 1 Randomized Clinical Trials Addressing Impact of Local Therapy for the Primary Tumor

Country	ClinicalTrials.gov Identifier	Accrual Period	N	Initial Therapy	Radiotherapy	Primary End Point
India	NCT00193778 ^a	2005–2012	350	Adriamycin, cyclophosphamide, 5-FU	If indicated	Time to progression
Japan	JCOG1017 ^b	2011–2016	410	Systemic therapy	Not addressed	Survival
USA and Canada	NCT01242800 ^c	2011–2016	368	Systemic therapy	Per standards for stage I–III	Survival
Turkey	NCT00557986 ^d	2008–2012	281	Surgery	For breast conservation	Survival
Thailand	NCT01906112 ^e	2013–2019	476	Surgery	Not addressed	Survival
Austria	NCT01015625 ^f	2010–2019	254	Surgery	Per standards for stage I–III	Survival

^aAssessing 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 trial ¹ (NCT00193778)

-- U.S. trial ² (NCT00941759)

Trials Requiring Randomization to Surgery Before Systemic Therapy

-- Turkish trial ³ (NCT00557986)

1. *Lancet Oncol.* 2015 Oct;16(13):1380-8.

2. 2016 ASCO Annual Meeting. Abstract 1006.

3. 2016 ASCO Annual Meeting. Abstract 1005.



3. Prospective trial evaluating locoregional surgery

Indian trial

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.



3. Prospective trial evaluating locoregional surgery

Indian trial

Overall survival analysis

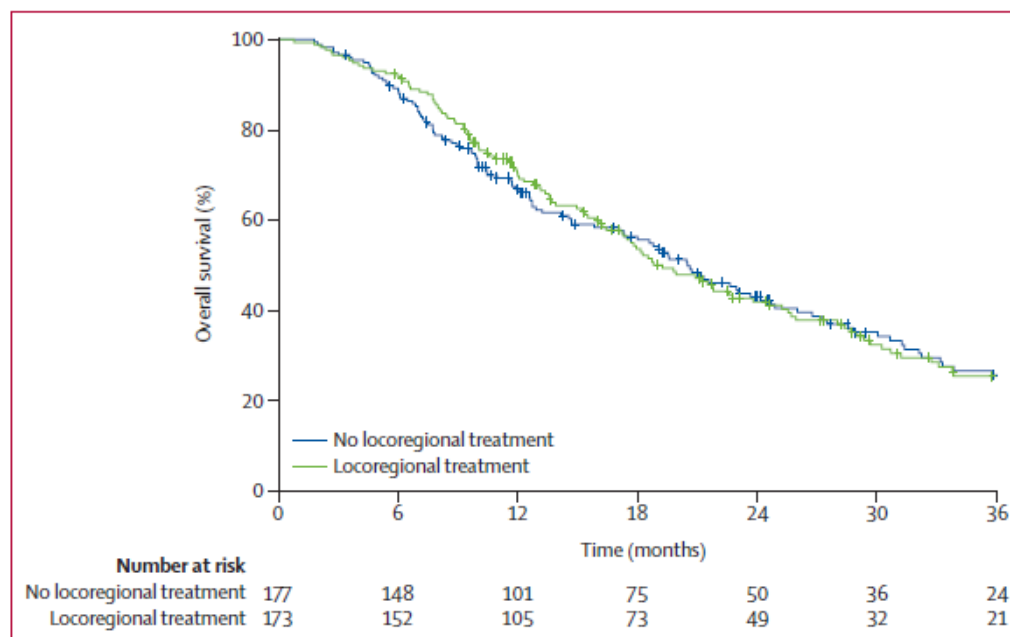


Figure 2: Kaplan-Meier plot of overall survival

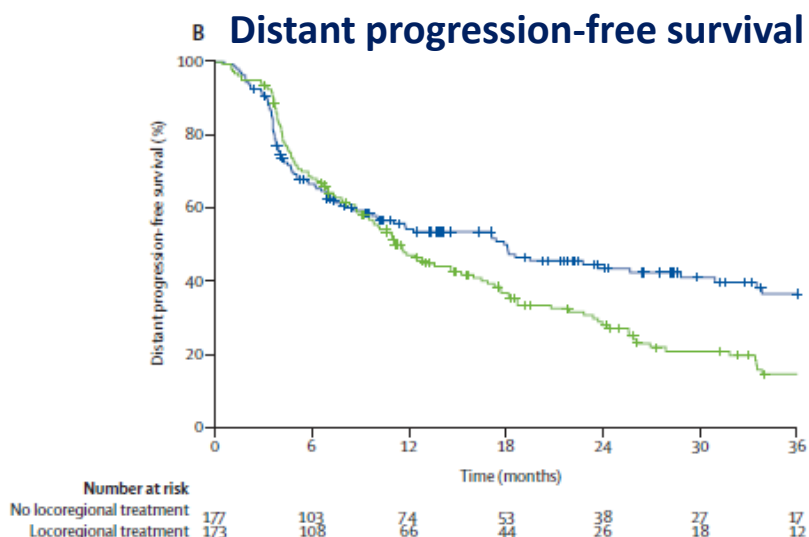
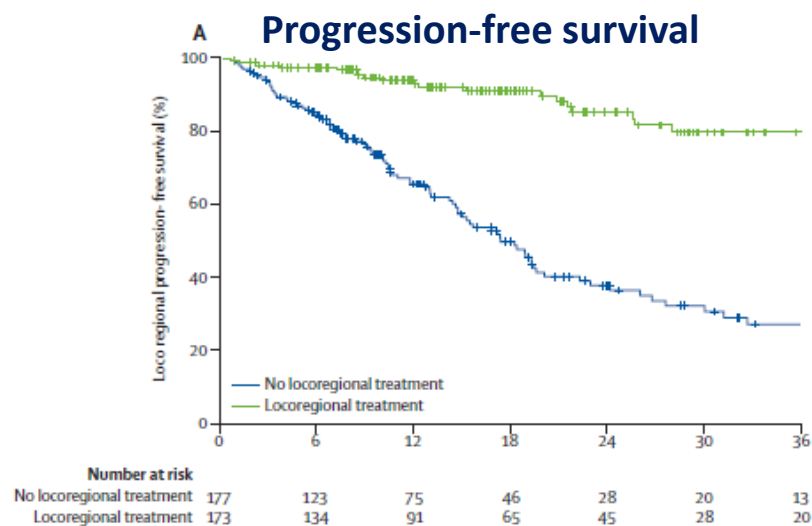
Locoregional treatment did not result in a significant improvement in **overall survival** compared with no locoregional treatment (median survival **19.2 months** [95% CI 15.98–22.46] vs **20.5 months** [16.96–23.98]; HR 1.04, 95% CI 0.81–1.34; p=0.79.

Lancet Oncol. 2015 Oct;16(13):1380-8.



3. Prospective trial evaluating locoregional surgery

Indian trial



(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 7.7–14.84] vs **19.8 months** [10.26–29.0]; HR 1.42, 95% CI 1.08–1.85; $p = 0.012$).

Lancet Oncol. 2015 Oct;16(13):1380-8.



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.

Responders	Surgery	N	Median Survival, mos (95%CI)	3yr OS (95%CI)	p
All	N	51	71 (56-NR)	76 (66-89)	0.85
	Y	39	77 (52-NR)	77 (65-91)	
ER+	N	46	71 (56-NR)	78 (67-91)	0.47
	Y	34	77 (53-NR)	79 (67-94)	
HER2+	N	12	NR (NR-NR)	83 (65-100)	0.39
	Y	15	77 (77-NR)	100 (100-100)	



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).



3. Prospective trial evaluating locoregional surgery

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)

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

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

Soran A, Ozmen V, Ozbas S, et al; 2016 ASCO Annual Meeting. Abstract 1005. Presented June 4, 2016.



3. Prospective trial evaluating locoregional 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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4. Retrospective data on metastases resection

Metastatic sites resection study

Clinical Research Paper

Hormone receptor status may impact the survival benefit of surgery in stage iv breast cancer: a population-based study

- 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**

Oncotarget. 2016 Oct 25;7(43):70991-71000.



4. Retrospective data on metastases resection

Metastatic sites resection study

Overall survival curves of the four groups

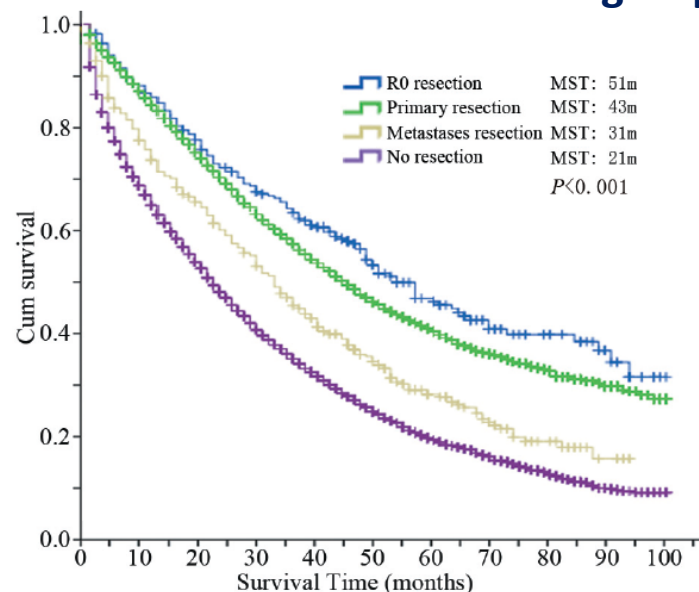


Figure 1: Overall survival curves of the four groups.

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

Survival curves of the four groups in the HR+ population

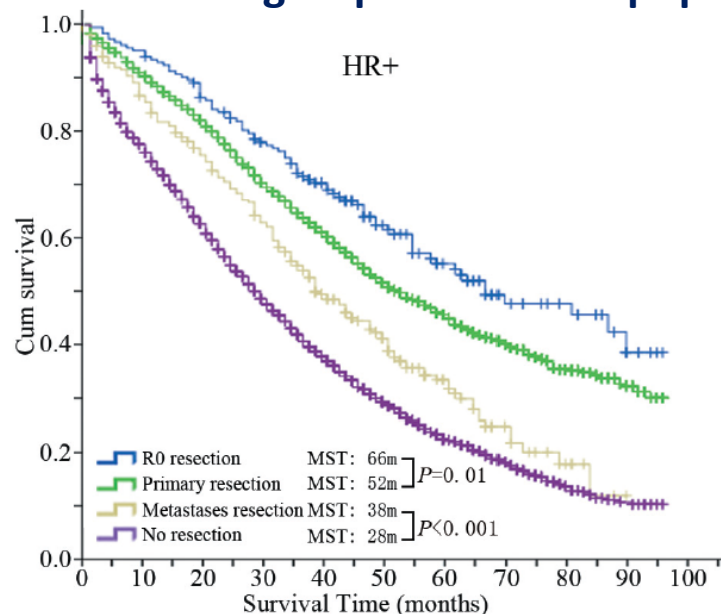


Figure 2: Kaplan-Meier survival curves of the four groups in the HR+ population.

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*).



4. Retrospective data on metastases resection

Metastatic sites resection study

Survival curves of the four groups in the HR- population

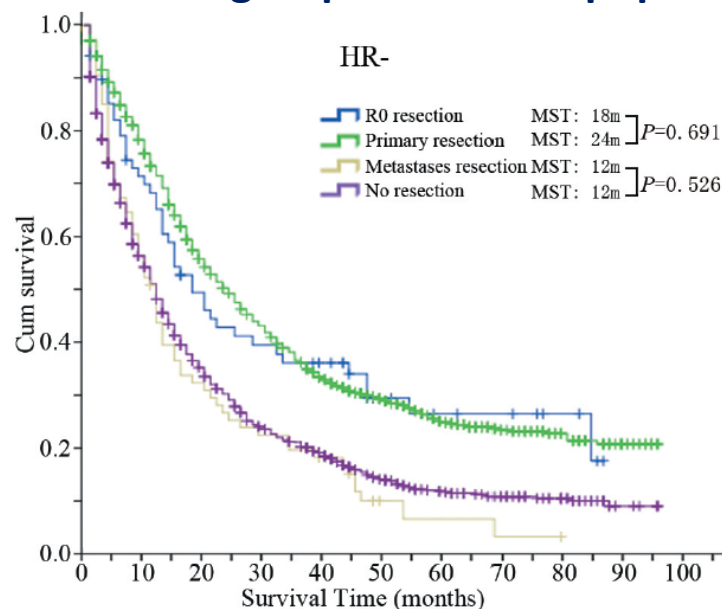


Figure 3: Kaplan-Meier survival curves of the four groups in the HR- population.

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%) ($P = 0.526$).

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4. Retrospective data on metastases resection

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.**



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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.

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Thank you!

