




SURGICAL THERAPY IN THE SETTING OF METASTATIC BREAST CANCER

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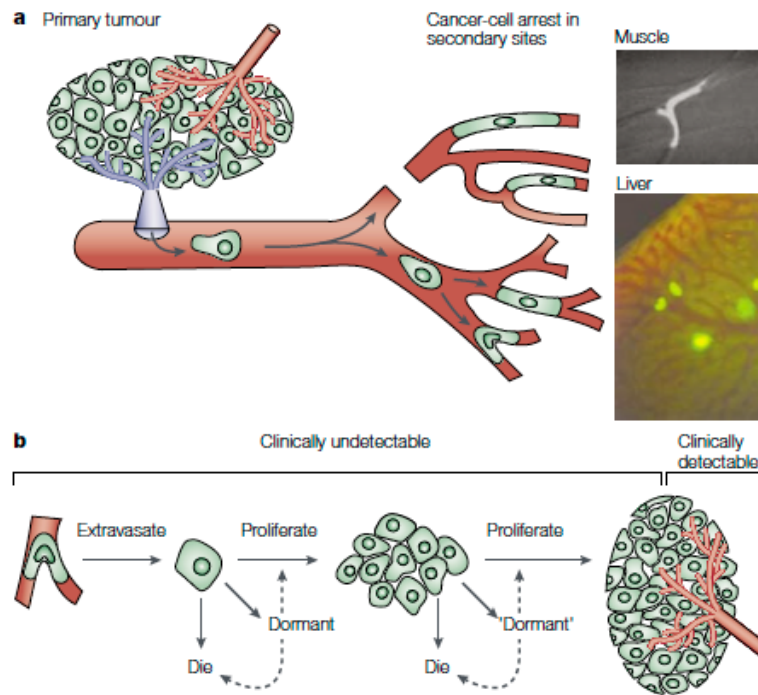
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How can surgery impact survival in metastatic breast cancer?

“Theories”



Cells released from primary tumor and proliferate, remain dormant, or die

How could surgery *positively* impact survival in metastatic breast cancer?

“Theories”

Control of seeding from primary tumor site¹

Decrease in formation of tumor stem cells within the primary tumor stroma²

Decrease in tumor-induced immunosuppression by the intact primary site^{3, 4}

¹Norton, Massague, Nat Med 2006

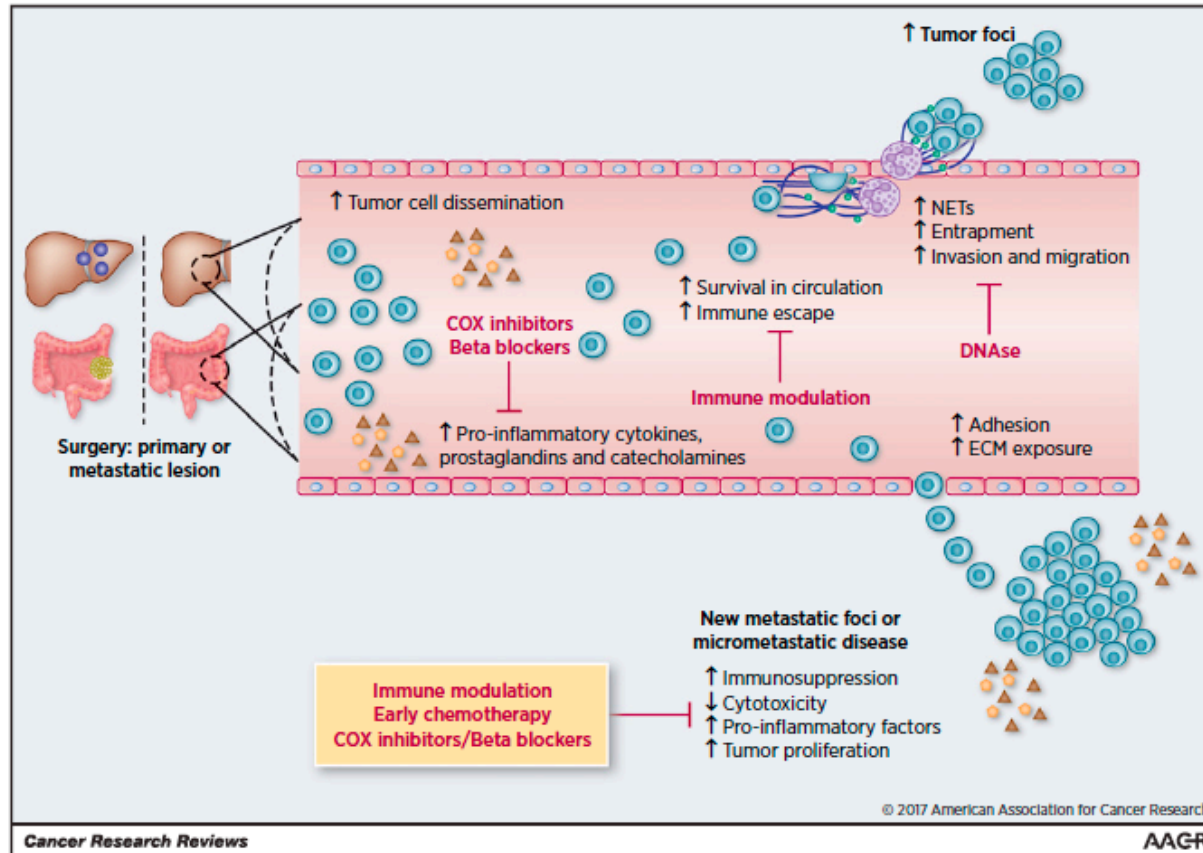
²Kamoub et al, Nature 2007

³Campbell et al, Breast Cancer Res Treat 2005

⁴Danna et al, Cancer Res 2004

How could surgery *negatively* impact survival in metastatic breast cancer?

“Theories”



Tumor removal promotes metastasis via multiple mechanisms¹

Stem cells may preferentially originate in metastatic lesions^{2,3}

¹Tohme, Cancer Res, 2017; ²Abraham, Clin Cancer Res, 2005;

³Balic, Clin Cancer Res, 2006

Surgery and metastatic breast cancer in the US

- Approximately 6% of breast cancer patients have metastatic disease
 - Approximately 25% of those present with de novo Stage IV disease
- Historically, surgery was limited to palliation of symptoms
 - Thus, most patients with metastatic disease were not offered surgery
 - A shift in attitude has gained momentum
 - Proven benefits of surgical intervention in other metastatic cancers (i.e., renal)
 - Studies showing a benefit for surgery in breast cancer
 - An ever-increasing population of patients living with metastatic breast cancer

Projected incidence of metastatic breast cancer in the US

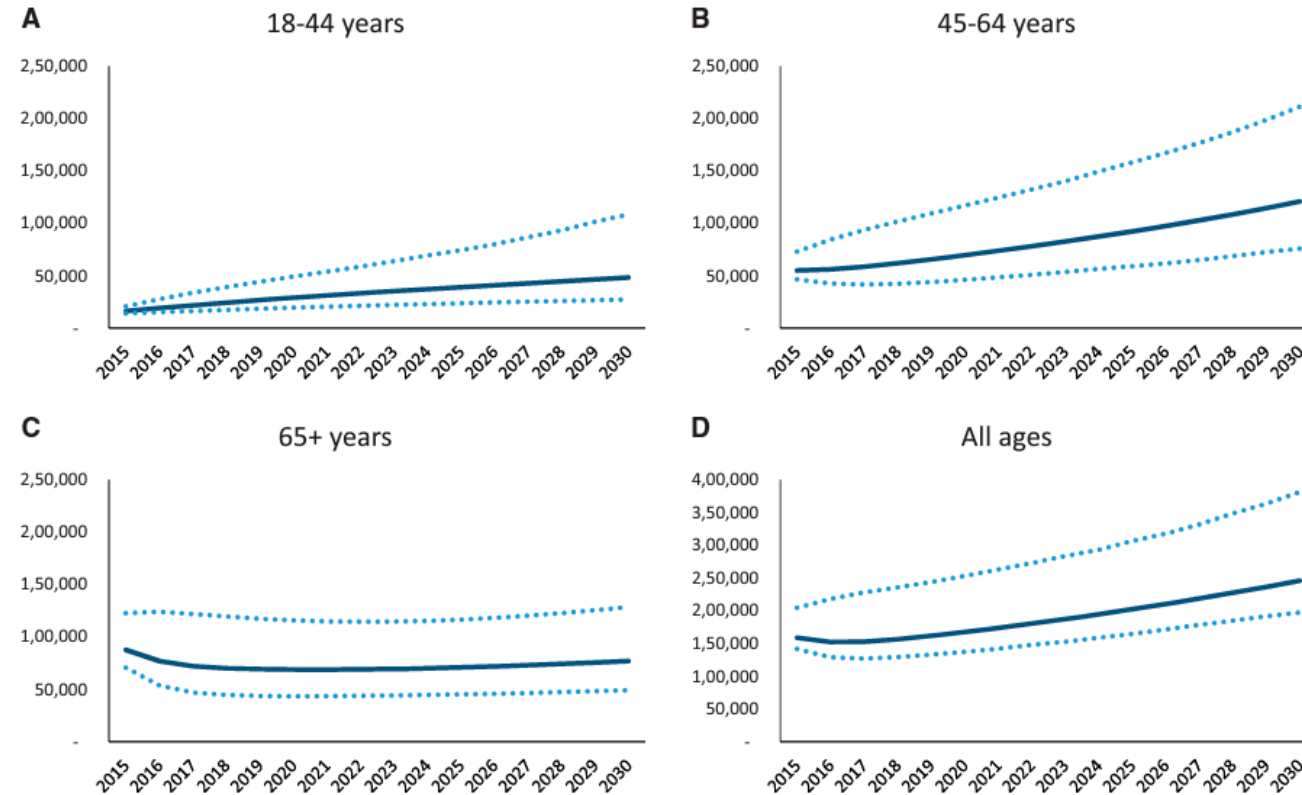


Figure 2. Prevalent metastatic breast cancer (mBC) case projections and 95% sensitivity ranges by age group, 2015-2030. This figure draws on inputs from US Census population projections, the Surveillance, Epidemiology, and End Results (SEER) Explorer and SEER Fast Stats databases. The annual progression rate from non-mBC to mBC was estimated from the published literature. These inputs were applied to a stock and flow model to estimate and project the number of prevalent mBC by age group from 2015 to 2030. A) 18- to 44-year-olds. B) 45- to 64-year-olds. C) 65+ year-olds. D) All ages. Solid = base case; dotted = 95% sensitivity ranges.

Metastatic Breast Cancer

Surgery for Metastatic Breast Cancer

Surgery for cure

- Removal of the intact primary tumor

Surgery for local control/palliation

- Prevention of a future problem or treatment of a current problem

Surgery/radiation for metastatic lesions

- I will defer this to the upcoming debate

Definitive Surgery for Relapse Metastatic Breast Cancer

Survival relapse versus de novo metastatic disease

- 2001-2009, British Columbia, 3645 patients

Table 2 Median overall survival (mOS) for entire metastatic breast cancer (MBC) cohort ($N = 2796$) and for cohort receiving some systemic therapy ($N = 2486$)

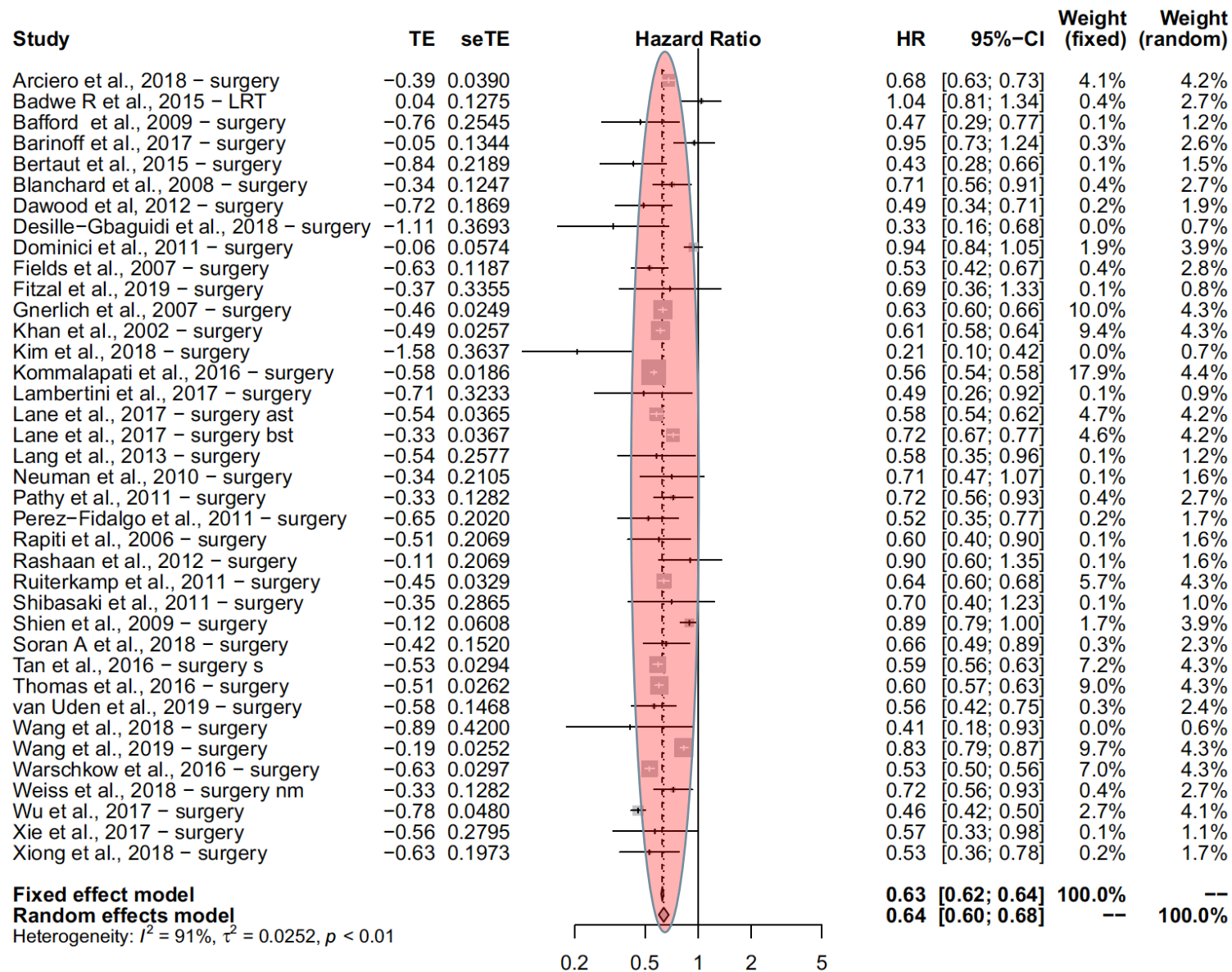
	Overall MBC cohort					PTS receiving some systemic treatment for MBC				
	Relapsed		De novo		<i>P</i> value	Relapsed		De novo		<i>P</i> value
	N	mOS (Q1, Q3) months	N	mOS (Q1, Q3) months		N	mOS (Q1, Q3) months	N	mOS (Q1, Q3) months	
ALL	2085	17 (6, 36)	711	29 (11, 59)	<0.0001	1818	20 (9, 40)	668	31 (13, 61)	<0.0001
HR+/HER2−	1174	23 (9, 44)	406	34 (15, 64)	<0.0001	1096	24 (12, 46)	403	34 (15, 65)	<0.0001
TN	444	8 (3, 18)	91	11 (5, 20)	0.02	318	10 (5, 21)	71	13 (8, 23)	0.04
HER2+ ALL	467	15 (6, 29)	214	29 (11, 59)	<0.0001	404	17 (7, 34)	194	31 (15, 61)	<0.0001
HR+	225	20 (6, 39)	112	34 (14, 64)	0.0002	204	23 (8, 43)	105	36 (19, 67)	0.0003
HR−	242	12 (5, 21)	102	23 (9, 42)	<0.0001	200	14 (7, 23)	89	26 (13, 49)	<0.0001

HER2 human epidermal growth factor 2, *HR* hormone receptor, *mOS* median overall survival, *MBC* metastatic breast cancer, *N* number, *Q1* first quartile, 75% of cases with tumor size greater than stated, *Q3* third quartile, 25% of cases with tumor size less than stated, *TN* triple negative, *yr*s years

Definitive Surgery for De Novo Stage IV Breast Cancer

Retrospective Studies: “Real World Experience”

Locoregional therapy of the primary tumour in de novo stage IV breast cancer in 216 066 patients: A meta-analysis

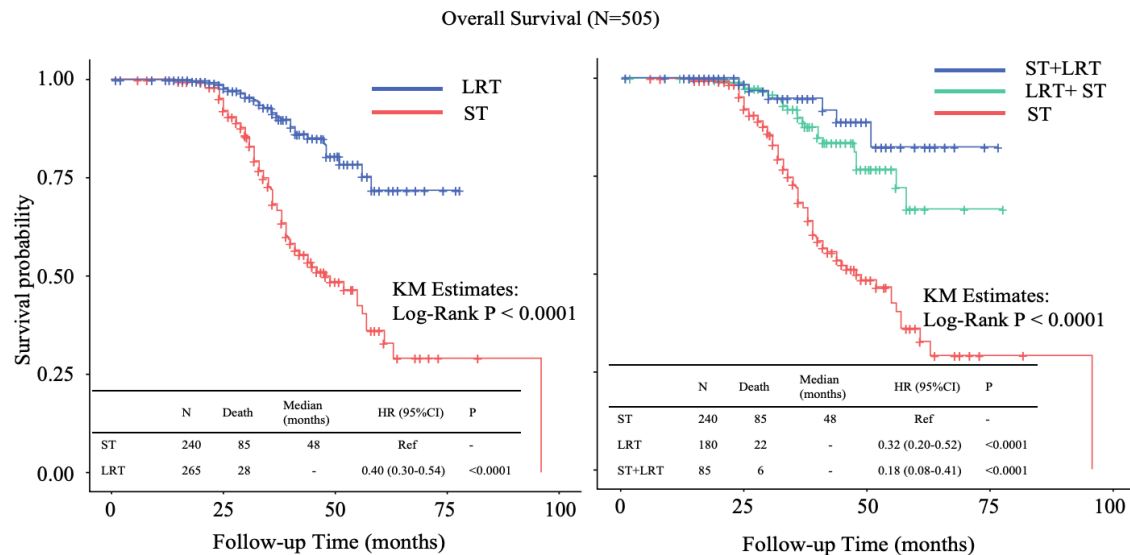


Issues:

- 1) Selection
- 2) Confounding
- 3) Immortal-time bias

Prospective Registry Trials: “Real, Real World Experience”

BOMET MF14-01



- 505 patients (240 surgery)
- Bone only metastasis (5.9% confirmed)
- Best survival was in the systemic therapy / surgery group
- Benefit of surgery
 - Yes: HR+, HER2-
 - No: TNBC

TBCRC Trial 013

- 112 patients – systemic therapy and then local therapy if deemed appropriate
- 3-year OS 71% (95 CI, 63-79)
 - Responders: 76-77%
 - No responders: 24%
- Surgery did not alter survival in either group

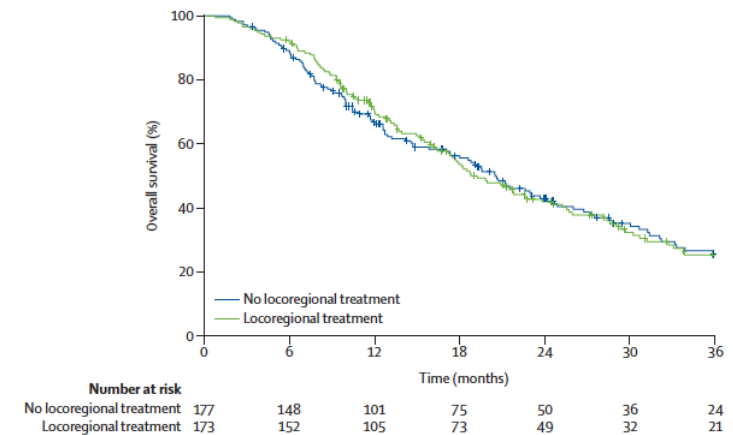
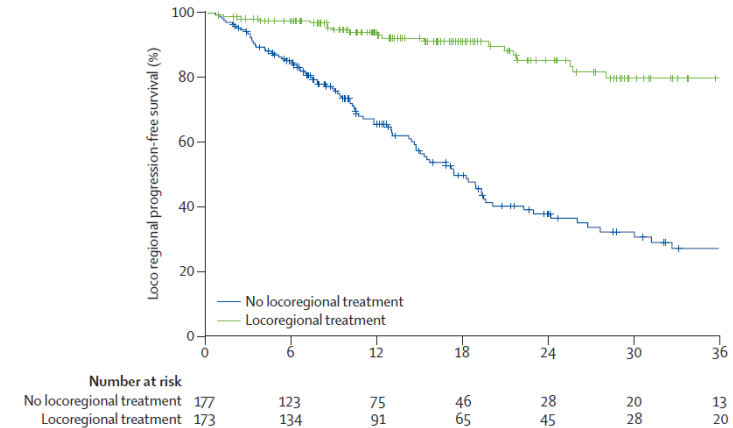
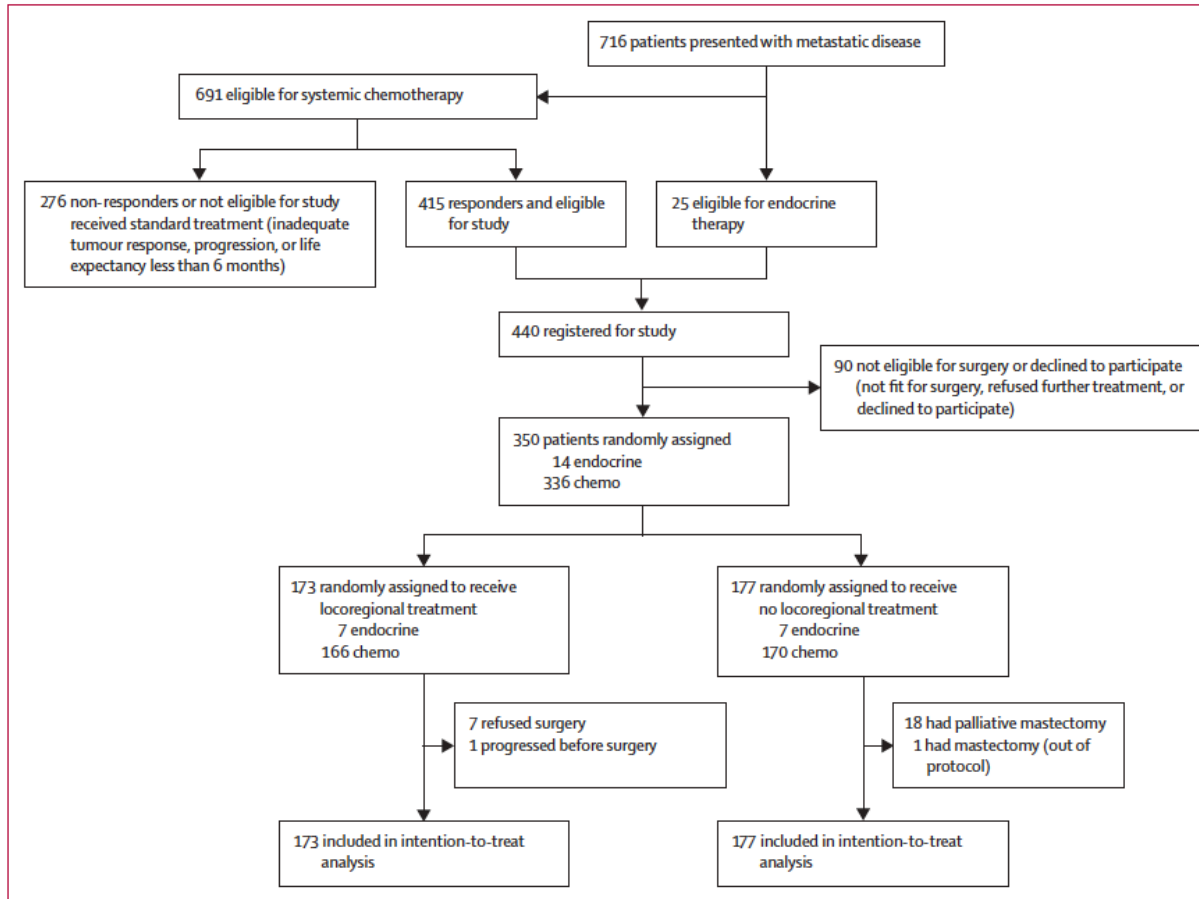
Table 3. Median TTP and 2-Year OS by Risk Group Among Patients With De Novo Stage IV Breast Cancer

	RS Risk Group			Log-Rank <i>P</i>
	Low Risk (RS < 18)	Intermediate Risk (RS 18-30)	High Risk (RS ≥ 31)	
TTP, months, median (range)				
All patients (n = 101)	NR (16-NR)	22 (16-NR)	16 (9-25)	.010
ER positive (n = 85)	32 (16-NR)	22 (16-NR)	15 (9-25)	.007
ER positive/HER2 negative (n = 69)	NR (16-NR)	20 (16-NR)	15 (8-27)	.003
2-Year OS, %				
All patients (n = 101)	100 (78-100)	100 (78-100)	80 (69-93)	.035
ER positive (n = 85)	100 (78-100)	100 (78-100)	77 (64-94)	.008
ER positive/HER2 negative (n = 69)	100 (78-100)	100 (75-100)	69 (51-93)	< .001

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NR, not reached; OS, overall survival; RS, Recurrence Score; TTP, time to first progression.

Prospective Trials: “The Gold Standard”

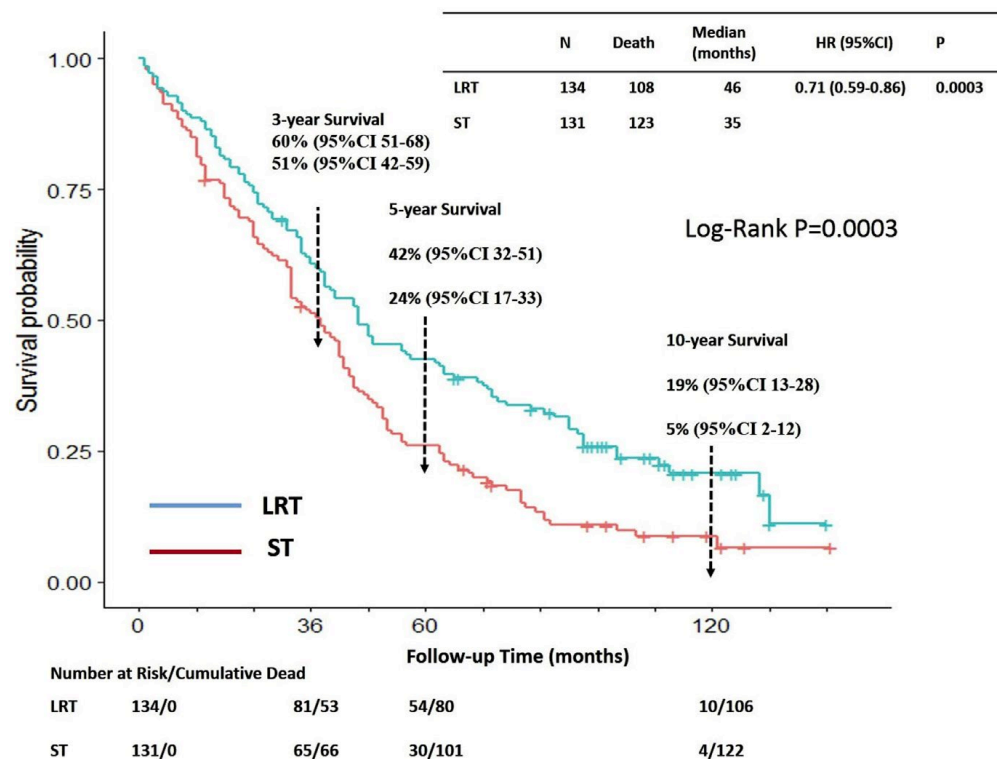
Locoregional Treatment versus No Treatment of the Primary Tumour in Metastatic Breast Cancer: an Open-Label Randomized Controlled Trial



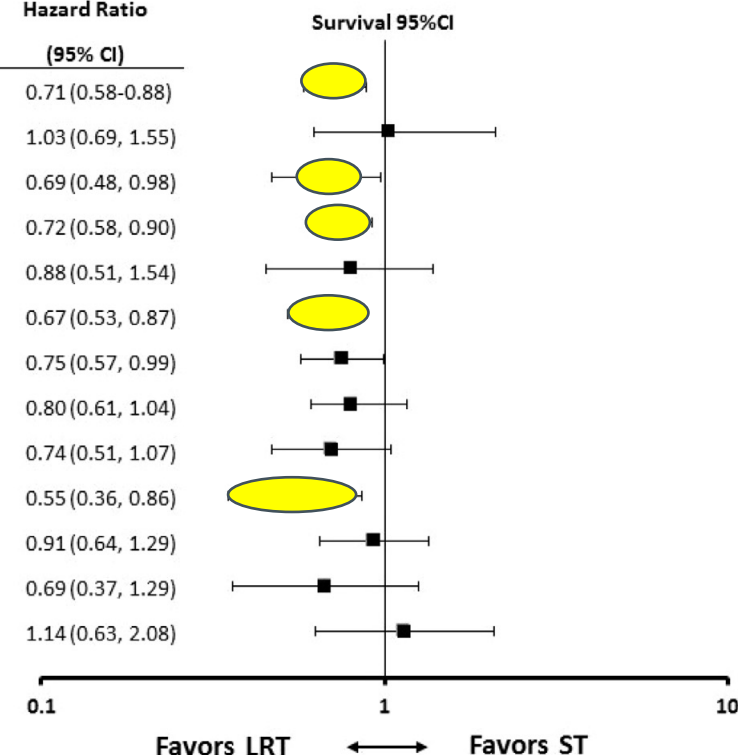
Locoregional control without a survival benefit

Badwe et al, Lancet Oncology, 2015

A Randomized Controlled Trial Evaluating Resection of the Primary Breast Tumor in Women Presenting with De Novo Stage IV Breast Cancer: Turkish Study (MF07-01) (10-year Follow-up)



Subgroup	LRT		ST		Hazard Ratio (95% CI)
	Event	Total	Event	Total	
ER_PR Positive	90	115	88	95	0.71 (0.58-0.88)
ER_PR Negative	18	19	34	35	1.03 (0.69, 1.55)
HER2 Positive	31	40	34	37	0.69 (0.48, 0.98)
HER2 Negative	77	94	88	93	0.72 (0.58, 0.90)
Triple Negative	9	10	21	23	0.88 (0.51, 1.54)
Age<55	61	76	70	76	0.67 (0.53, 0.87)
Age≥55	47	58	53	55	0.75 (0.57, 0.99)
Bone only Met	59	68	50	54	0.80 (0.61, 1.04)
Other Mets noBone	23	34	40	43	0.74 (0.51, 1.07)
Solitary Bone Met	28	31	19	19	0.55 (0.36, 0.86)
Multiple Bone Met	31	37	31	35	0.91 (0.64, 1.29)
Solitary Pulmonary/Liver Met	8	13	14	15	0.69 (0.37, 1.29)
Multiple Pulmonary/Liver Met	10	13	12	14	1.14 (0.63, 2.08)



HR(+), HER2(+) = better
TNBC and/or liver/lung mets = worse

Impact of Breast Surgery in Primary Metastasized Breast Cancer Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial

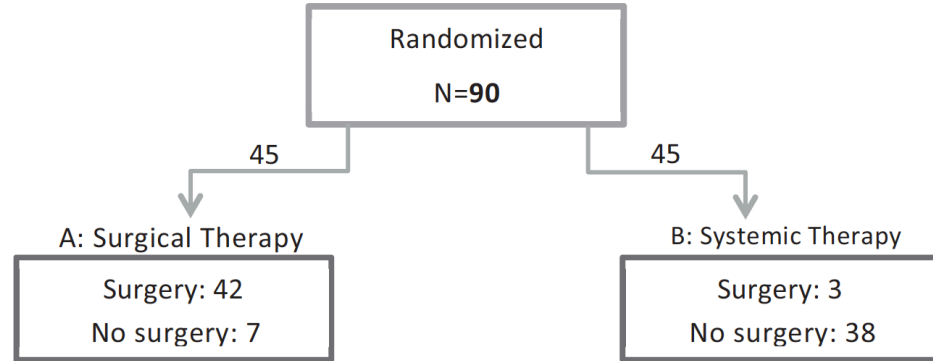
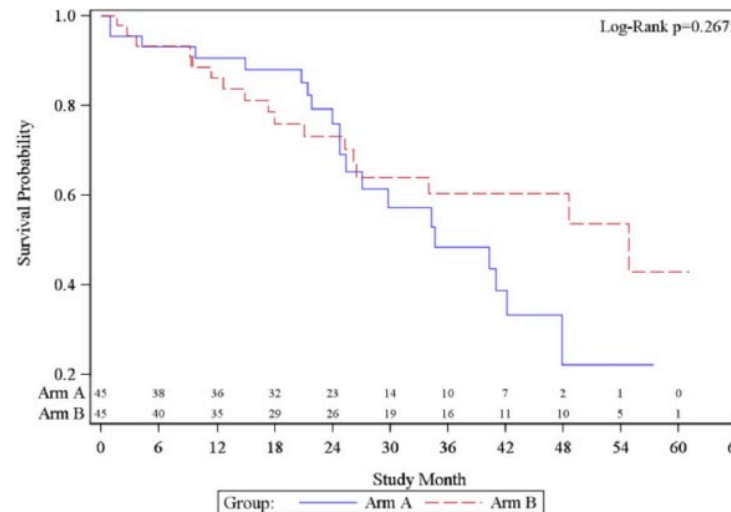
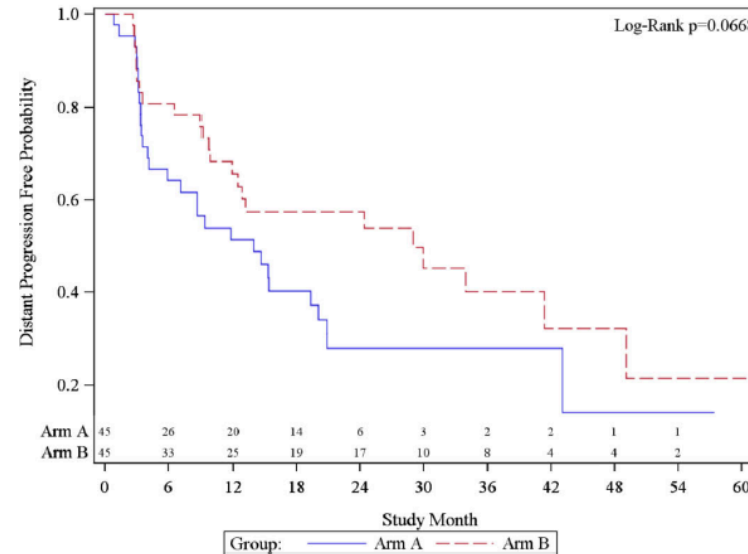


TABLE 2. Systemic Treatment Data

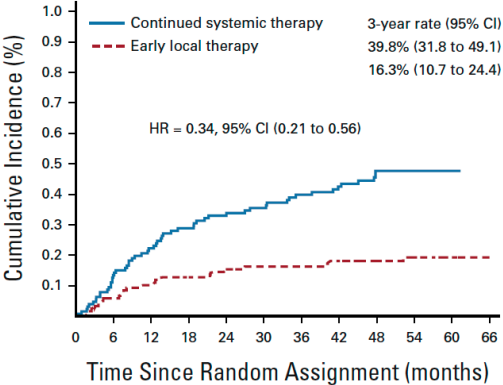
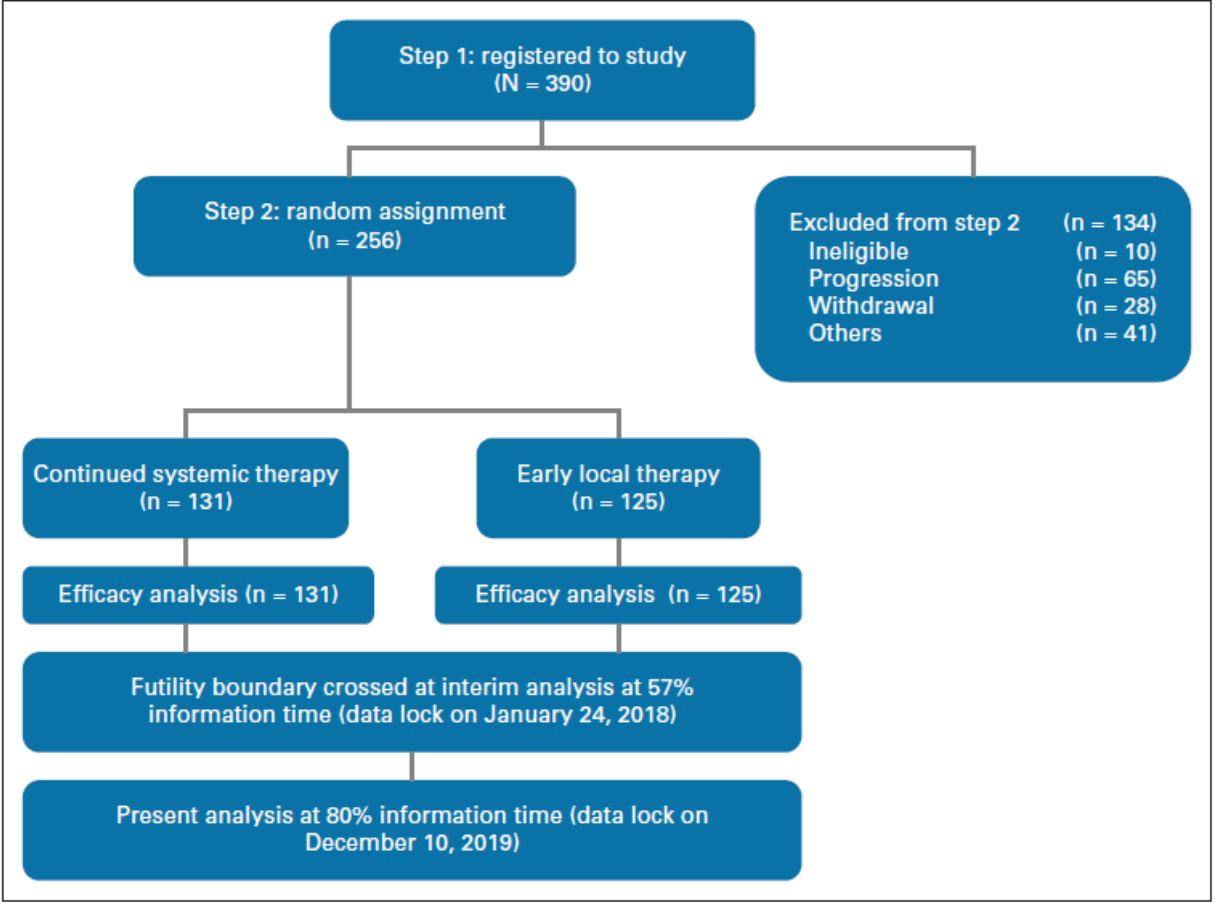
	Arm A Surgical Therapy n = 45 (%)	Arm B No Surgical Therapy n = 45 (%)	P*
Given first-line therapy			
Any Chemo no Taxane	8 (18)	6 (13)	0.588
Any Chemo with Taxane	7 (16)	11 (24)	
Endocrine therapy	30 (67)	28 (62)	
Radiotherapy			
Breast/chest wall	9 (20)	2 (4.4%)	0.021
Metastasis	18 (40)	12 (27)	0.619 [†]
Surgery			
Metastases	2 (4.4)	3 (6.7)	1.00

*Fisher exact test.
[†]Between number of patients who had radiotherapy of metastasis.



Maybe luminal B better???

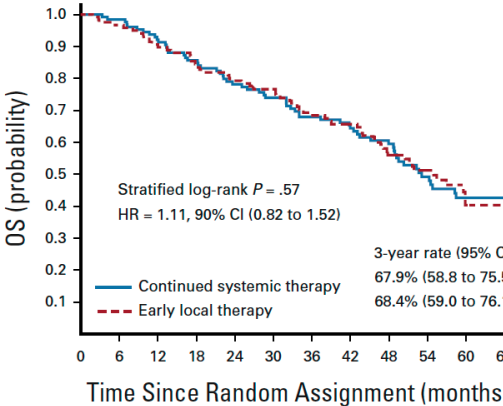
Early Local Therapy for the Primary Site in De Novo Stage IV Breast Cancer: Results of a Randomized Clinical Trial (EA 2108)



No. at risk:

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66
Continued systemic therapy	131	108	89	75	67	59	50	44	30	21	3	1
Early local therapy	125	107	95	89	80	74	67	61	47	33	9	3

Local control improved

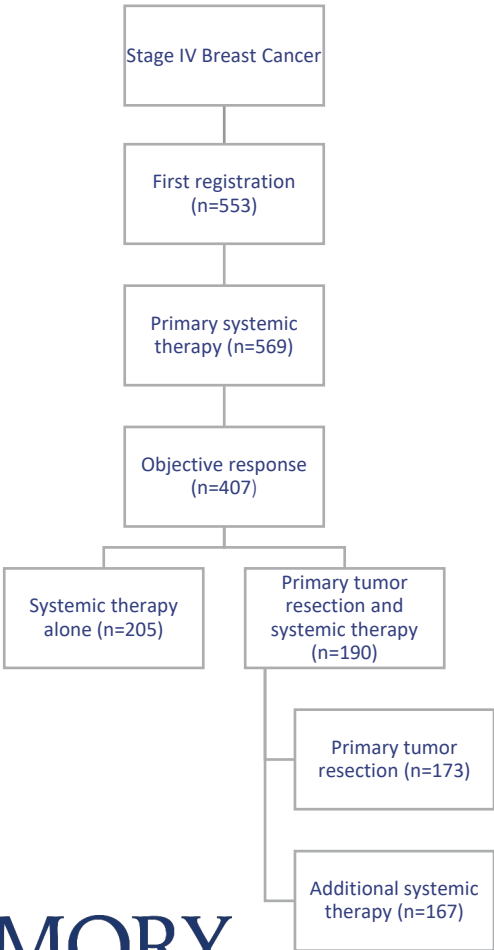


No. at risk:

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66
Continued systemic therapy	131	125	115	105	93	87	77	71	58	40	12	3
Early local therapy	125	112	103	97	91	85	75	70	54	36	8	2

No subgroup had an increase in OS

A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group study JCOG1017



	Systemic therapy	Primary tumor resection and systemic therapy
5-year OS (95% CI)	55.4% (48.2-62.0)	62.5% (55.3-68.8)
Median OS (95% CI)	68.7 months (55.7-81.1)	74.9 months (65.7-95.4)
HR (95% CI) p value	0.857 (0.686-1.072) 0.3129	

- 1) Local control was improved with surgery
- 2) Resection did not prolong survival
- 3) Positive margins led to worse survival (HR 1.971 (1.161-3.347) p=0.012)
- 4) Maybe there is a role in pre-menopausal woman and/or those with limited metastasis

Surgery for De Novo Stage IV Breast Cancer

- **Local control**
 - Proven benefit in local control – *but to what end?*
- **Survival**
 - Only in retrospective studies and one prospective trial
 - Maybe there are subsets of patients that may benefit
 - 1) Premenopausal women?
 - 2) Oligometastatic disease (bone only)?
 - 3) Hormone positive disease?*****these are patients that are already going to have a better survival*****
- **There are likely groups that will not benefit**
 - 1) TNBC
 - 2) Patients with a heavy metastatic burden or visceral metastasis

Surgery as a Part of Palliative Care for Metastatic Breast Cancer

Surgery For Palliation

- Palliation of symptoms is the goal
- Palliative surgery for the symptomatic primary tumor is indicated in only 6-16% of all patients
- American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database
 - Metastatic versus non-metastatic patients undergoing surgery
 - Significantly higher risk of complications (infection, thromboembolic, respiratory, cardiac, bleeding) (OR 1.6, 95% CI 1.2-2.1)
 - 7.5% versus 3.7%, $p < 0.001$
 - All-cause 30-day mortality also increased (1.8 versus 0.06%, $p < 0.001$)

Surgery For Palliation

- Analysis of SEER, 3660 patients with T4M1 disease
 - 43% underwent local therapy [surgery (19%) or radiation (15%) or both (9%)]
 - Most underwent mastectomy
- Outcomes
 - Potential benefit for those who present with significant morbidity
 - All others, symptoms are equivalent or worse after local therapy

Table 5 Comparison of rates of loco-regional morbidity in patients who were asymptomatic prior to local therapy ($n = 1435$) and patients who did not undergo local therapy ($n = 2102$)

Symptom	New morbidity after LT in asymptomatic patients prior to LT ($n = 1435$)	Baseline morbidity in patients not undergoing LT ($n = 2102$)	<i>P</i> value
Bleeding	≤ 10 (0.0%)	≤ 10 (0.0%)	0.563
Cellulitis	48 (3.3%)	18 (0.9%)	< 0.001
Abscess	37 (2.6%)	40 (1.9%)	0.177
Brachial plexopathy	22 (1.5%)	14 (0.7%)	0.012
Axillary neuropathic pain	≤ 10 (0.0%)	≤ 10 (0.0%)	1
Wound dehiscence	≤ 10 (0.0%)	NA	NA
Cancer-related pain	98 (6.8%)	50 (2.4%)	< 0.001
Lymphedema	58 (4.0%)	≤ 10 (0.0%)	< 0.001
Seroma	14 (1.0%)	NA	NA
Any symptom	285 (19.9%)	141 (6.3%)	< 0.001

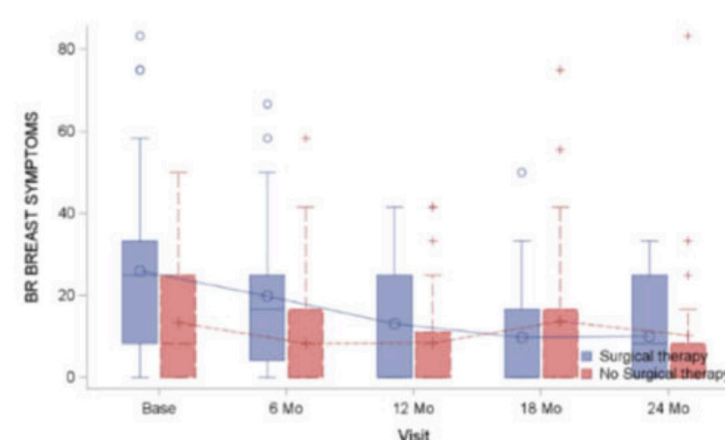
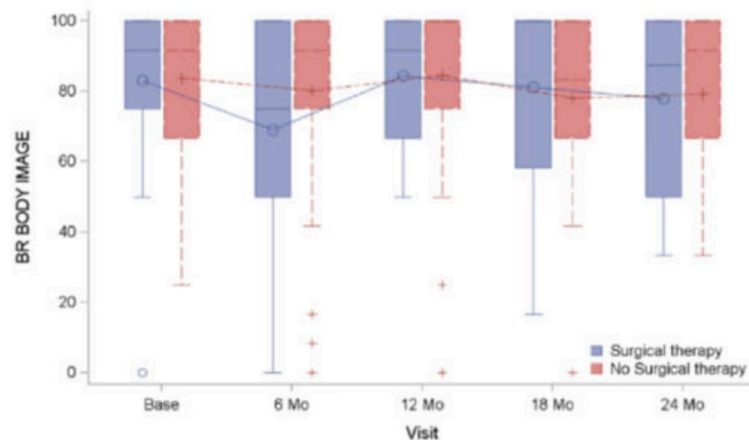
LT local therapy

* χ^2 test or Fisher's exact test if $n \leq 10$



ABCSG-28 Positive Trial: Quality of Life Outcomes

- 90 patients with de novo metastatic breast cancer randomized to surgery or no surgery
 - EORTC QLQ-C30 and QLQ BR23 surveys administered
- There was no improvement in quality of life for the surgery group
- Global health status and physical functioning played more of a role in overall survival than local therapy



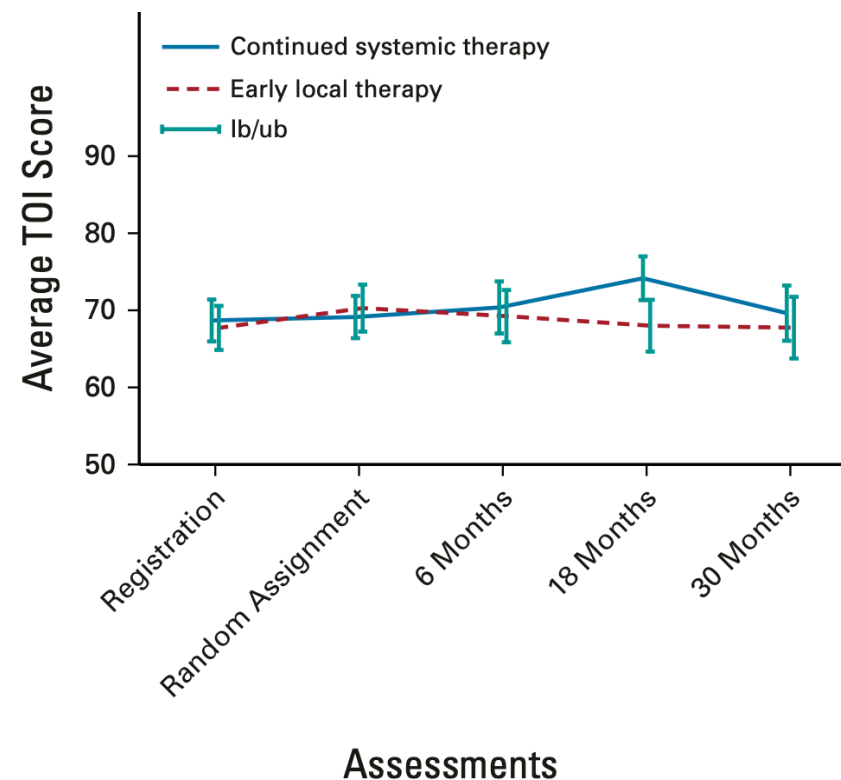
The role of loco-regional treatment in long-term quality of life in de novo stage IV breast cancer patients: protocol MF07-01Q

Table 3 Comparison of PCS-12 scores and MCS-12 scores and physical and mental health, daily activities, and energy level currently vs. at diagnosis of breast cancer (BC) in patients who lived ≥ 3 years between the groups

	LRT ¹ (n = 55)	ST only ² (n = 26)	Stage I–III BC (n = 201)	p ³	General population
^a PCS-12 score mean \pm SE	40.8 \pm 1.6	43.4 \pm 2.0	51.1 \pm 0.5	< 0.0001	49.3 \pm 0.1
^b MCS-12 score mean \pm SE	44.2 \pm 1.3	45.6 \pm 1.6	45.7 \pm 0.6	0.49	46.8 \pm 0.1
^c Age < 55					
PCS-12 score mean \pm SE	43.3 \pm 1.7	44.4 \pm 1.8	50.8 \pm 0.5	< 0.0001	
MCS-12 score mean \pm SE	43.2 \pm 1.3	47.0 \pm 1.3	46.4 \pm 0.6	0.11	
^d Age ≥ 55					
PCS-12 score mean \pm SE	36.3 \pm 1.4	42.2 \pm 2.1	52.0 \pm 0.6	< 0.0001	
MCS-12 score mean \pm SE	46.0 \pm 1.3	43.8 \pm 1.8	43.7 \pm 0.6	0.61	
^e Age < 65					
PCS-12 score mean \pm SE	40.9 \pm 1.4	43.9 \pm 2.0	51.3 \pm 0.5	< 0.0001	
MCS-12 score mean \pm SE	44.2 \pm 1.3	44.9 \pm 1.5	46.0 \pm 0.5	0.40	
^f Age ≥ 65					
PCS-12 score mean \pm SE	39.9 \pm 1.4	38.9 \pm 2.5	47.6 \pm 0.7	0.18	
MCS-12 score mean \pm SE	43.9 \pm 1.5	50.9 \pm 1.6	41.7 \pm 0.7	0.39	
	LRT ¹ (n = 55)	ST ² (n = 26)		p	
	% (n)	% (n)			
Current physical health vs. at diagnosis of breast cancer	Same = 49% (27) Better = 11% (6) Worse = 40% (22)	Same = 50% (13) Better = 23% (6) Worse = 27% (7)		0.27	
Current mental health vs. at diagnosis of breast cancer	Same = 55% (30) Better = 20% (11) Worse = 25% (14)	Same = 42% (11) Better = 31% (8) Worse = 27% (7)		0.49	
Current daily activities vs. at diagnosis of breast cancer	Same = 18% (10) Better = 47% (26) Worse = 35% (19)	Same = 23% (6) Better = 50% (13) Worse = 27% (7)		0.75	
Current energy vs. at diagnosis of breast cancer	Yes = 45% (25) No = 55% (30)	Yes = 50% (13) No = 50% (13)		0.70	

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer: ECOG-ACRIN 2108

- FACT-B TOI was the primary HRQoL endpoint
- Measured by the prorated aggregate score of the 24 items from the FACT-B
- FACT-B TOI was significantly lower in patients receiving early local therapy at 18 months post randomization
- No significant difference was found between arms at other assessment time points



No. at risk:

Continuous systemic therapy	104	113	98	65	62
Early local therapy	102	106	88	66	49

Surgery for Palliation

Is local therapy justified for the metastatic breast cancer patient?

- **Symptomatic – maybe**
- **Asymptomatic – clearly no**

The key is palliation!

Surgery in Metastatic Breast Cancer

- **For improvement in survival: No.....but maybe after a substantial response to upfront systemic therapy?**

Subsets for potential:

- 1) **Oligometastatic – bone only met? treatable met?**
- 2) **Primary progressive but mets gone?**
- 3) **Rendered NED with systemic therapy?**

Subsets to be avoided:

- 1) **TNBC**
- 2) **Visceral mets / heavy distant disease burden**
- 3) **Recurrent metastatic disease**

Surgical resection of the primary tumor in metastatic breast cancer should be in selected cases only and only after multidisciplinary discussion.

¶¶¶ Routine surgical resection of the primary breast tumor is generally not indicated in the management of patients presenting with de novo stage IV (M1) disease. Although there is no survival benefit, it may be considered for local control of the primary tumor. Discussion regarding management of the primary tumor in this setting must be individualized.



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