Surgery in Metastatic Disease: Is There a Role?

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Reason for Surgery

- Palliation of symptoms
  - Main indication
- Improved survival ?

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RCTs: Two basic designs

TABLE 1 Phase III trials evaluating the overall survival impact of local therapy for the intact primary tumor in women with Stage IV breast cancer

Study	Accrual period	*n*	Overall survival HR (95 % CI)	Locoregional progression-free survival HR (95 % CI)
Trials requiring response or stable disease to initial systemic therapy				
Badwe (India)	2005–12	350	1.04 (0.84–1.34)	0.16 (0.10–0.26)
Khan (USA, Canada)	2011–15	256	1.11 (0.82–1.52)	0.35 (0.21–0.57)
Shien (Japan)	2011–16	407	Not reported	Not reported
Initial randomization to PSLT or systemic therapy				
Soran (Turkey)	2008–12	274	0.66 (0.49–0.88)	1 % vs 11 %
Fitzal (Austria)	2010–19	93	0.69 (0.36–1.33)[a]	8.9 % vs 17.8 %

HR, hazard ratio; CI, confidence interval; PSLT, primary-site local therapy

[a]Favored systemic therapy arm

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Khan SA, Schuetz S, Hosseini O 2022

Turkish Trial MF07-01

- 274 patients, 2002-2012, Multiple centers across Turkey
- Randomization prior to therapy.
- Locoregional treatment was mastectomy or breast conservation (26%) and SLNB was allowed if cN0, however 90% required ALND. This was followed by standard adjuvant radiation as per nonmetastatic protocols.
  - Systemic therapy was given after surgical intervention

Soran et al, 2018

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TABLE 1 Patient, tumor characteristics, treatment, and metastatic site distribution

	LRT (n = 138) n (%)	ST (n = 136) n (%)	p value
Mean age (years)	51.8 ± 12.6	51.5 ± 13.6	0.87
Mean BMI (kg/m^2)	27.6 ± 5.2	27.8 ± 6.0	0.70
Mean follow-up (months)	40.5 ± 22.0	35.8 ± 21.7	0.08
Median follow-up (25, 75%)	41.0 (24, 54)	37 (18, 49)	0.10
Tumor size (%)			0.23
T1	12 (8.7)	11 (8.1)	
T2	72 (52.2)	58 (42.7)	
T3	30 (21.7)	30 (22.1)	
T4	24 (17.4)	37 (27.2)	
Histologic grade (%)			0.16
1	6 (4.4)	10 (9.6)	
2	55 (39.9)	33 (31.7)	
3	77 (55.8)	61 (58.9)	
Tumor type (%)			0.26
Invasive ductal	110 (79.7)	115 (84.6)	
Invasive lobular	15 (10.9)	13 (9.6)	
Mixed tumor type	13 (9.4)	8 (5.8)	
ER/PR(+) (%)[a]	118 (85.5)	97 (71.8)	0.01
HER2/neu(+) (%)[b]	42 (30.4)	42 (31.1)	0.90
Triple-negative (%)	10 (7.3)	23 (17.4)	0.01
Treatment (%)			
BCS + axillary evaluation	36 (26)	–	NA
M + axillary evaluation	102 (74)	–	NA
SLNB[c]	23 (17)	–	NA
ALND	128 (92.8)	–	NA
Positive LN	123 (89.1)	–	NA
Intervention to metastasis	35 (25)	48 (35)	0.07
Anthracycline-based CT	127 (92.0)	120 (89)	0.38
Bisphosphonates	37 (26.8)	32 (23.5)	0.53
Metastasis site (%)			0.17
Bone only	71 (51)	55 (40)	
Bone + others	33 (24)	37 (27)	
Others (no bone)	34 (25)	44 (32)	
Solitary/multiple metastasis (%)			0.71
Solitary bone	33 (34)	20 (24)	
Multiple bone	38 (39)	35 (41)	
Solitary pulmonary or liver	13 (13)	15 (18)	
Multiple pulmonary or liver	13 (13)	15 (18)	

LRT locoregional treatment, *ST* systemic therapy, *BMI* body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* HER2/neu, *BCS* breast-conserving surgery, *NA* not applicable, *M* mastectomy, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *LN* lymph node, *CT* chemotherapy

[a]Patients with ER/PR(+) tumor received hormonal therapy

[b]Patients with HER2/neu(+) received trastuzumab

[c]SLNB(+) patients underwent ALND

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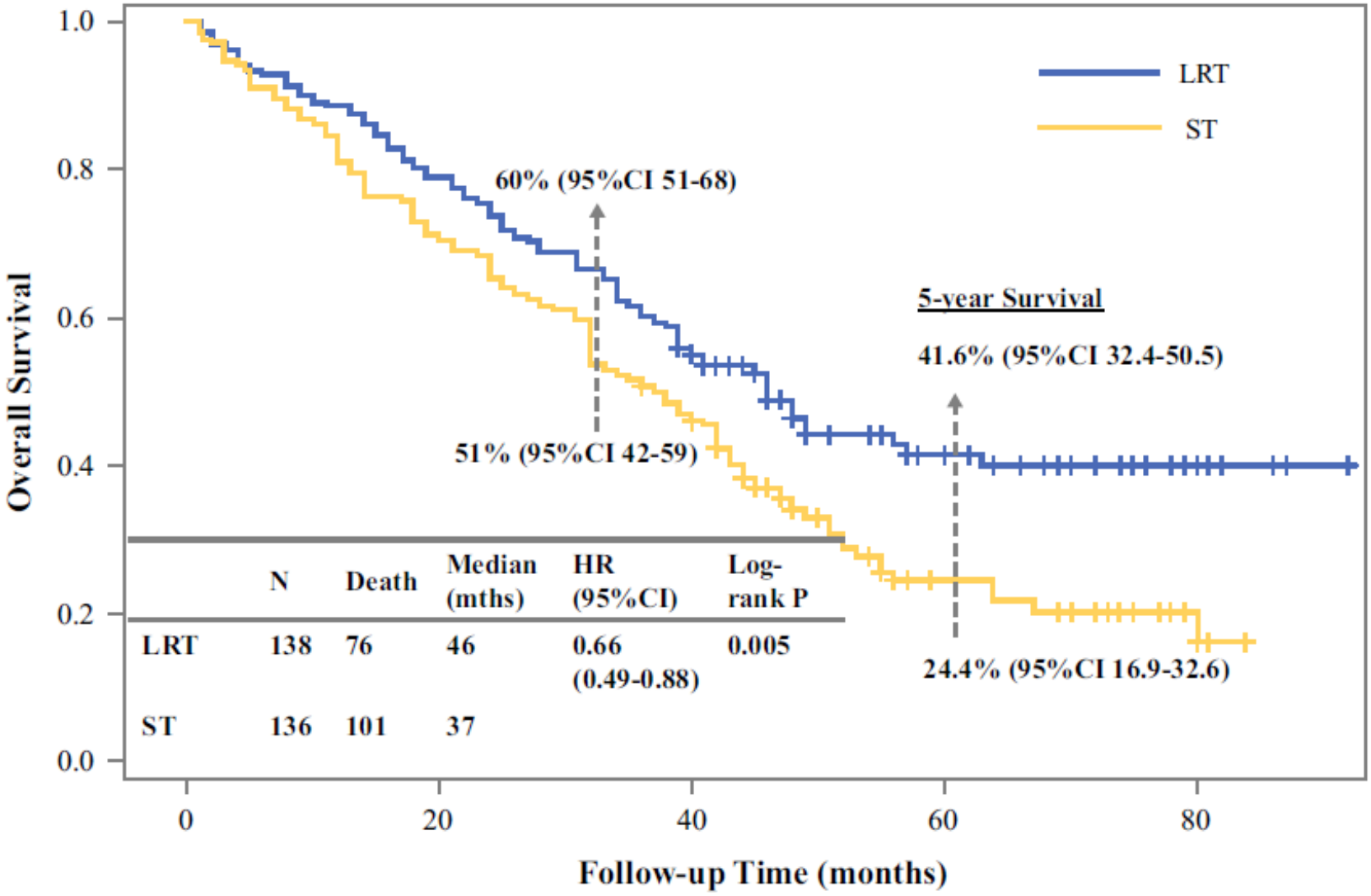

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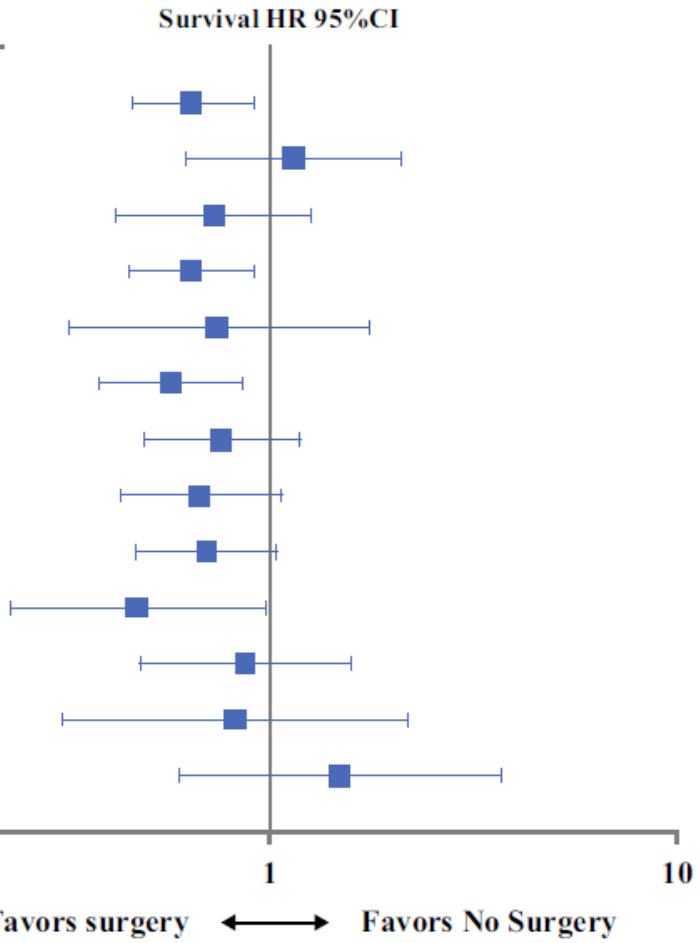
Subgroup	Surgery Event	Surgery Total	No Surgery Event	No Surgery Total	Hazard Ratio (95% CI)
ER/PR Positive	59	118	69	97	0.63 (0.44, 0.89)
ER/PR Negative	31	38	30	36	1.22 (0.67, 2.23)
HER2 Positive	23	42	29	42	0.73 (0.42, 1.26)
HER2 Negative	53	96	71	93	0.64 (0.45, 0.91)
Triple Negative	7	10	21	23	0.74 (0.32, 1.75)
Age<55	39	79	59	80	0.57 (0.38, 0.86)
Age≥55	37	59	42	56	0.76 (0.49, 1.18)
Bone only Met	36	71	37	55	0.67 (0.43, 1.07)
Other Mets noBone	40	67	64	81	0.7 (0.47, 1.04)
Solitary Bone Met	14	33	15	20	0.47 (0.23, 0.98)
Multiple Bone Met	22	38	22	35	0.87 (0.48, 1.58)
Solitary Pulmonary/Liver Met	7	13	10	15	0.82(0.31, 2.18)
Multiple Pulmonary/Liver Met	9	13	10	15	1.49 (0.60, 3.72)



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Soran et al, 2018

Indian Trial TATA

- 716 patients, 2005-2013, de-novo metastatic breast cancer At Tata Memorial Centre Mumbai India
- Randomization after initiation of systemic therapy. Most patients (96%) received pre-randomization chemotherapy with an anthracycline based combination chemotherapy. Endocrine therapy was also given as indicated.
- Excluded women >65, expected survival < 1yr, extensive liver metastasis, limited metastatic disease amendable to local therapy.
- Local regional treatment was mastectomy or breast conservation and axillary lymph node dissection. Superclavicular dissection was performed for persistent or residual lymph nodes. This was followed by standard adjuvant radiation as per nonmetastatic protocols.
  - Bilateral oophorectomy was performed In hormone receptor positive patients who had menstrual cycles after chemotherapy.
- Salvage mastectomy for symptom palliation was required in 10% of the systemic therapy patients.

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Badwe et al, 2015

	Locoregional treatment group (n=173)	No locoregional treatment group (n=177)
Age (years)		
Median	48	48
Site of metastasis		
Bone	50 (29%)	50 (28%)
Visceral	75 (43%)	77 (44%)
Bone and visceral	48 (28%)	50 (28%)
Number of metastases		
≤3	44 (25%)	45 (26%)
>3	129 (75%)	132 (74%)
Oestrogen receptor or progesterone receptor		
Negative	71 (41%)	71 (40%)
Positive	102 (59%)	106 (60%)
Menopausal status†		
Pre and peri	74 (43%)	88 (50%)
Post	99 (57%)	89 (50%)
HER2 status		
Negative (including 1+)	124 (72%)	108 (61%)
Positive (3+)	45 (26%)	62 (35%)
Not known or equivocal (2+)	4 (2%)	7 (4%)

Data are n (%) unless stated otherwise. †Perimenopausal: history of no menstruation up to one preceding year; postmenopausal: cessation of menstrual cycles for more than 1 year.

Table 1: **Baseline characteristics of the intention-to-treat population**

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Badwe et al, 2015

	Locoregional treatment group	No locoregional treatment group
Upfront randomly assigned and received pre-randomisation endocrine treatment	7/173 (4%)	7/177 (4%)
Aromatase inhibitor	5/7 (71%)	4/7 (57%)
Tamoxifen	2/7 (29%)	3/7 (43%)
Received pre-randomisation chemotherapy	166/173 (96%)	170/177 (96%)
CAF/CEF	159/166 (96%)	161/170 (95%)
Anthracycline plus taxane	6/166 (4%)	9/170 (5%)
Paclitaxel plus carboplatin	1/166 (1%)	0/170 (0%)
HER2-targeted treatment in HER2 3+ patients	1/45 (2%)	0/62 (0%)
Eligible for post- randomization endocrine treatment	102/173 (59%)	106/177 (60%)
Aromatase inhibitor	51/102 (50%)	46/106 (43%)
Tamoxifen	50/102 (49%)	60/106 (57%)
Not received	1/102 (1%)	0/106 (0%)
Premenopausal or perimenopausal women with hormone responsive tumours	49/74 (66%)	58/88 (66%)
Ovarian suppression		
Surgical (bilateral salpingoophorectomy)	38/49 (78%)	21/58 (36%)
Medical	0/49 (0%)	1/58 (2%)
Radiation	0/49 (0%)	17/58 (29%)
Not done	11/49 (22%)	19/58 (33%)

Data are n (%).

Table 2: **Systemic treatment before progression**

	Locoregional treatment group (n=173)	No locoregional treatment (n=177)
Surgery		
Modified radical mastectomy	125 (72%)	1 (1%)
Breast-conserving surgery	40 (23%)	NA
No surgery	8 (5%)	176 (99%)
Palliative surgery upon progression	1 (1%)	18 (10%)
Radiotherapy		
Chest wall and breast with supraclavicular fossa	119 (69%)	NA
Chest wall alone	19 (11%)	NA
No radiotherapy	8 (5%)	NA
Not known	27 (16%)	..

NA=not done.

Table 4: **Details of locoregional treatment**

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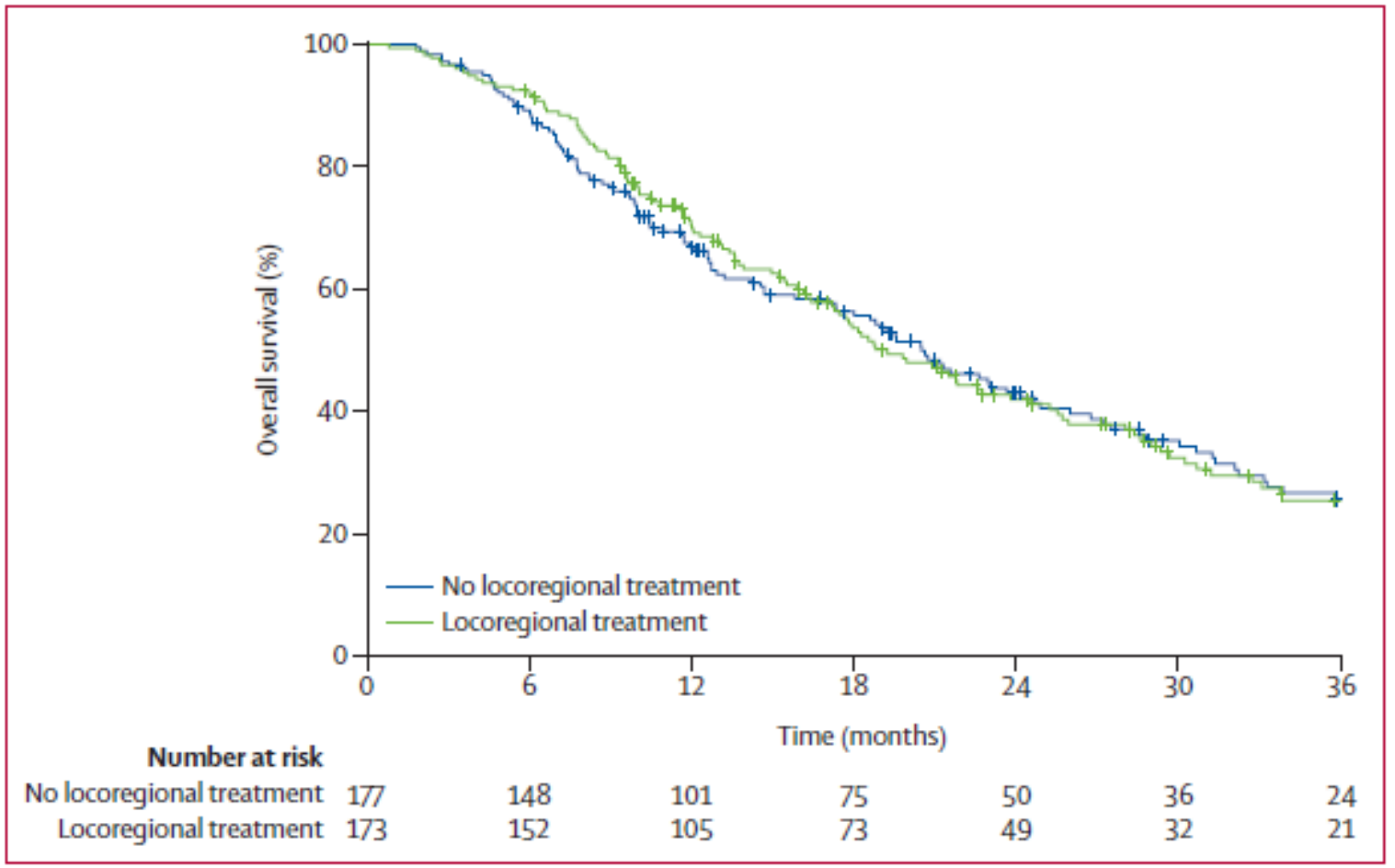

Figure 2: **Kaplan-Meier plot of overall survival**

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Badwe et al, 2015

USA/ Canada, ECOG E2108

- 256 patients , 2011-2015, multiple centers in USA and Canada.
- Randomization after initiation of systemic therapy, given for 16 to 32 weeks. Endocrine therapy alone was given in 31% of patients. Patients who progressed were not randomly assigned.
- Excluded expected survival <6mths
- Locoregional therapy was mastectomy or breast conservation with SLNB allowed in cN0 patients and ALND if involved nodes. This was followed by standard adjuvant radiation as per nonmetastatic protocols.
- Salvage mastectomy for symptom palliation was required in 13% of the systemic therapy patients.

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TABLE 2. Patient and Tumor Characteristics of Randomly Assigned Population, by Arm

Patient Characteristic	Continued Systemic Therapy (n = 131)[a]	Early Local Therapy (n = 125)[a]
Median age, years (range)	56 (25-86)	55 (30-81)
Race, No. (%)		
White	102 (82.3)	98 (82.4)
Black	19 (15.3)	19 (16.0)
Others	3 (2.4)	2 (1.7)
Missing	7	6
Ethnicity, No. (%)		
Non-Hispanic	103 (88.0)	106 (91.4)
Hispanic	14 (12.0)	10 (8.6)
Missing	14	9
Menopausal status at random assignment, No. (%)		
Postmenopausal	88 (71.0)	81 (69.2)
Pre- or perimenopausal	36 (29)	36 (30.8)
Missing	7	8
Breast cancer subtype, No. (%)		
Hormone receptor-positive and HER2-negative	73 (58.4)	73 (60.8)
Triple-negative	11 (8.8)	9 (7.5)
HER2-positive	41 (32.8)	38 (31.7)
Missing	6	5
Metastatic sites at random assignment, No, (%)		
Visceral only	14 (11.1)	13 (10.7)
Bone only	56 (44.4)	47 (38.8)
Soft tissue only	2 (1.6)	3 (2.5)
Multiple sites	40 (31.8)	44 (36.4)
Other single sites	4 (3.2)	3 (2.5)
No metastatic site	10 (7.9)	11 (9.1)
Missing	5	4

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TABLE 1. Patient, Tumor, and Treatment Characteristics of Registered and Randomly Assigned Populations (continued)

Patient Characteristic	Registered (N = 390)[a]	Not Randomly Assigned (n = 134)[a]	Randomly Assigned (n = 256)[a]	P
No	298 (79.9)	97 (75.8)	201 (82.0)	
Missing	17	6	11	
Optimal systemic therapy, No. (%)				.044
Endocrine therapy alone	117 (31.1)	40 (31.5)	77 (31.2)	
Chemotherapy alone	113 (30.2)	47 (37.0)	66 (26.7)	
Both endocrine and chemotherapy	39 (10.4)	15 (11.8)	24 (9.7)	
Chemotherapy with HER2-directed therapy	105 (28.1)	25 (19.7)	80 (32.4)	
Missing	16	7	9	

TABLE 3. Locoregional Therapy Data for Randomly Assigned Participants

Locoregional Therapy Details	Continued Systemic Therapy (n = 131)	Early Local Therapy (n = 125)
Breast surgery, No (%)	22 (16.8)	107[a] (85.6)
Breast conservation	7 (5.3)	31 (24.8)
Mastectomy	15 (11.5)	76 (60.1)
Axillary surgery, No (%)		
None	114 (87.0)	9 (7.2)
SN biopsy alone	5 (3.8)	13 (10.4)
Axillary dissection with or without SN biopsy	12 (9.2)	82 (65.6)
Locoregional radiotherapy, No (%)	15 (11.5)	72 (57.6)
After breast conservation	3 (2.3)	27 (21.6)
After mastectomy	7 (5.3)	44 (35.2)
Without surgery	5 (3.8)	0

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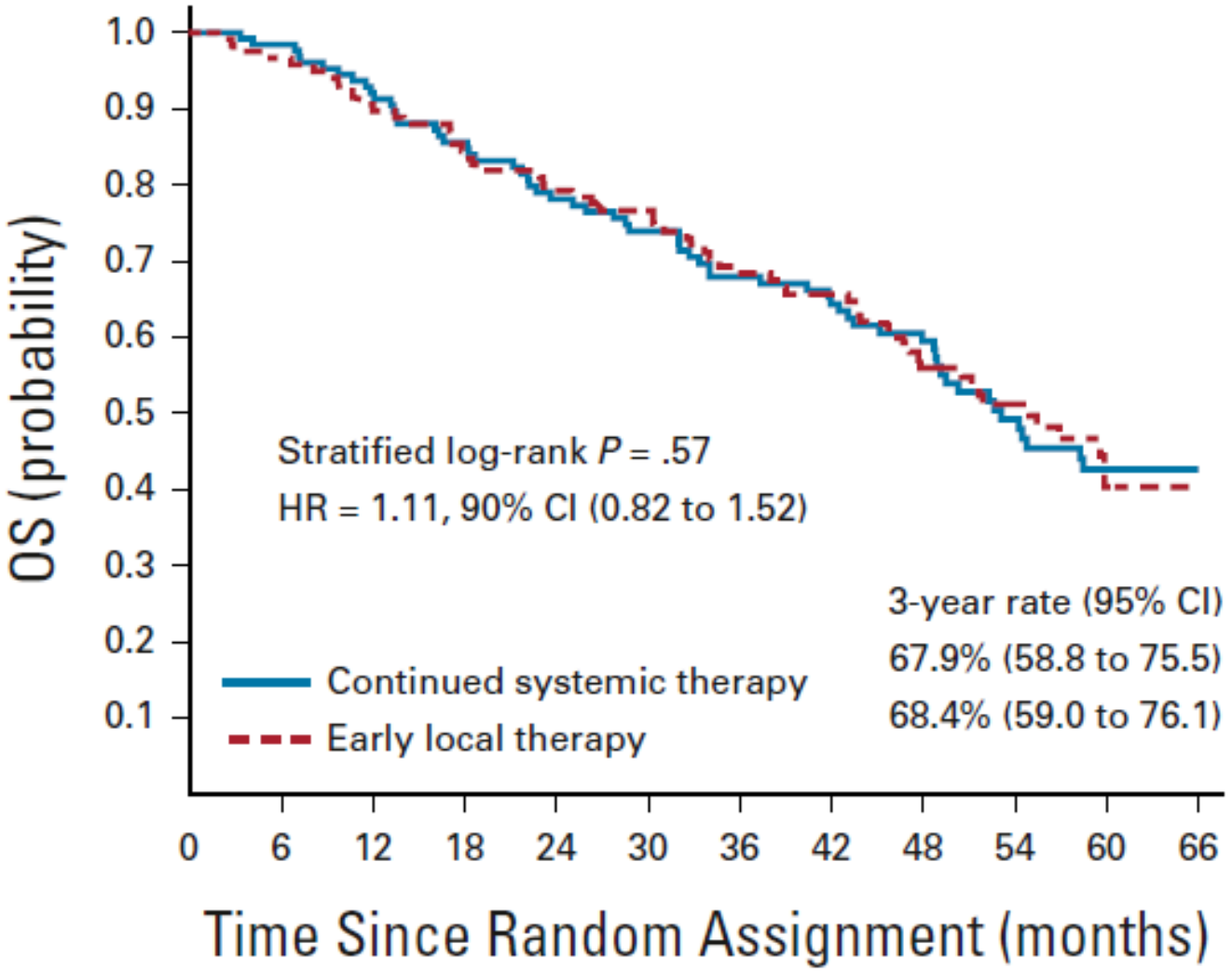

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Other Trials

- Austrian Trial POSYTIVE
  - Early termination, closed with 90/254 planned patients accrued in 4 years.
- Netherlands Trial
  - Closed due to accrual
- Thailand Trial
  - Closed due to accrual
- Japanese Trail
  - Results expected 2023

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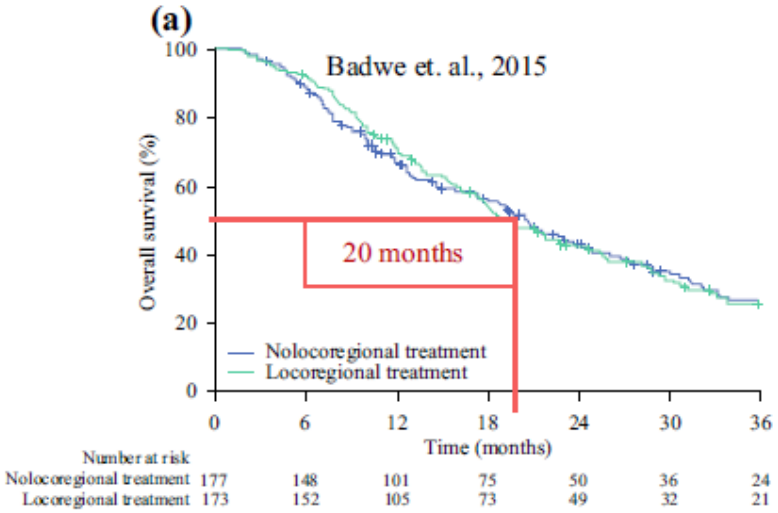

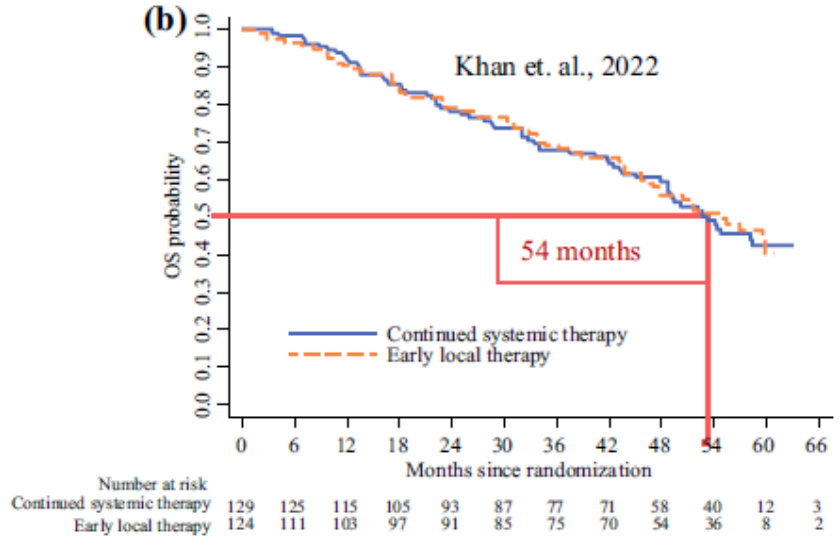

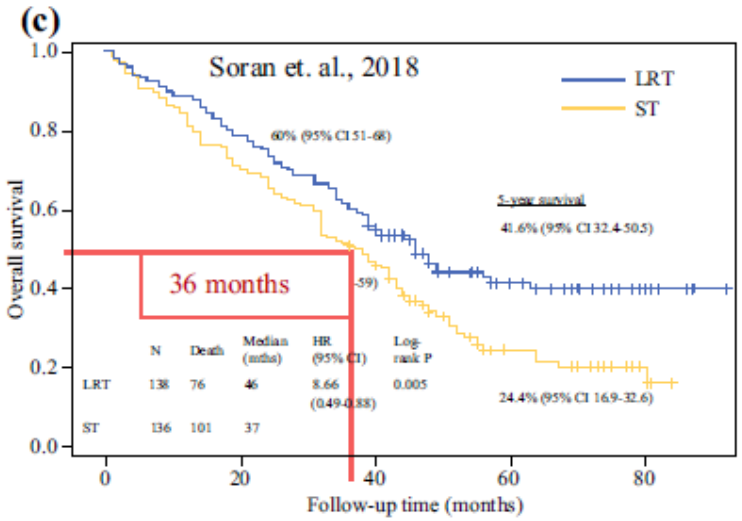

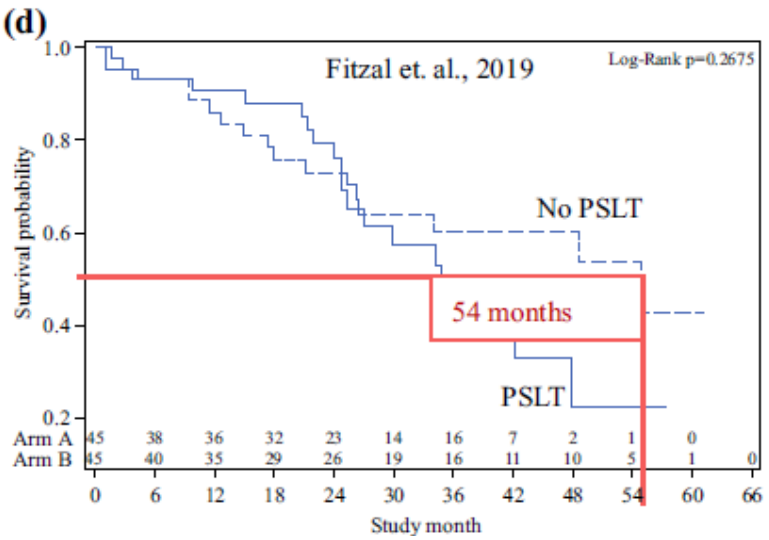

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Comparison of trials

MF 07-01 vs E2108

TABLE 2 Comparison of tumor characteristics in two randomized trials with discrepant results, conducted in an adequate resource environment

	MF 07-01		E2108	
	LRT arm	ST arm	LRT arm	ST arm
Randomized *n*	135	135	125	131
Average age (years)	52		57 years	
HR-positive (%)	**86**	72	57	59
HER2+ tumors (%)	30	30	30	30
Triple-negative (%)	7	**17**	9	8
Bone-only metastases (%)	**51**	40	38	38
Bone + visceral (%)	24	27	40	41
Oligometastases (%)[a]	**47**	24	17	15
Overall survival (years) (%)				
3	60	51	68	68
5	40	24	40	40

Bold values indicate imbalance between arms

[a]In MF07-01, this represents a combination of solitary metastasis in bone, lung, or liver. In E2108, it is composed of patients with ≤3 lesions in a single-organ system.

- Overall studies suggest that Local regional therapy does not have a large impact in overall survival.
- These studies show the importance of systemic therapy.
- Differences between trials may be due to imbalance in the arms of the Turkish trial.

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Quality of life

E2108

- QoL measurements at multiple time points.
- Functional Assessment of Cancer Therapy Breast questionnaire.
- Similar across five time points except at 18 months which favored the systemic therapy arm.

MF07-01

- QoL measurements at every six months.
- SF36 questionnaire
- Similar across time points

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Khan SA, Schuetz S, Hosseini O 2022, Khan et al, 2021, Soran et al, 2018

Retrospective Reviews

- Multiple retrospective reviews have been done which overall show and overall survival hazard ratio approximately 0.7 favoring the local therapy group.
- These studies suffer from selection bias.

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Scenarios to Consider

- Controlled distant disease but primary tumor progression
- Bone only or low volume metastatic disease
  - BOMET MF 14-01
- Contralateral axillary metastasis only
  - M1, Stage 4 but must exclude second primary.
  - CAM may be present at time of local recurrence due to lymphatic drainage changes caused by prior treatments.
  - Surgery is controversial due to low level of data but often surgical resection is offered.

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Magnoni et al, 2020

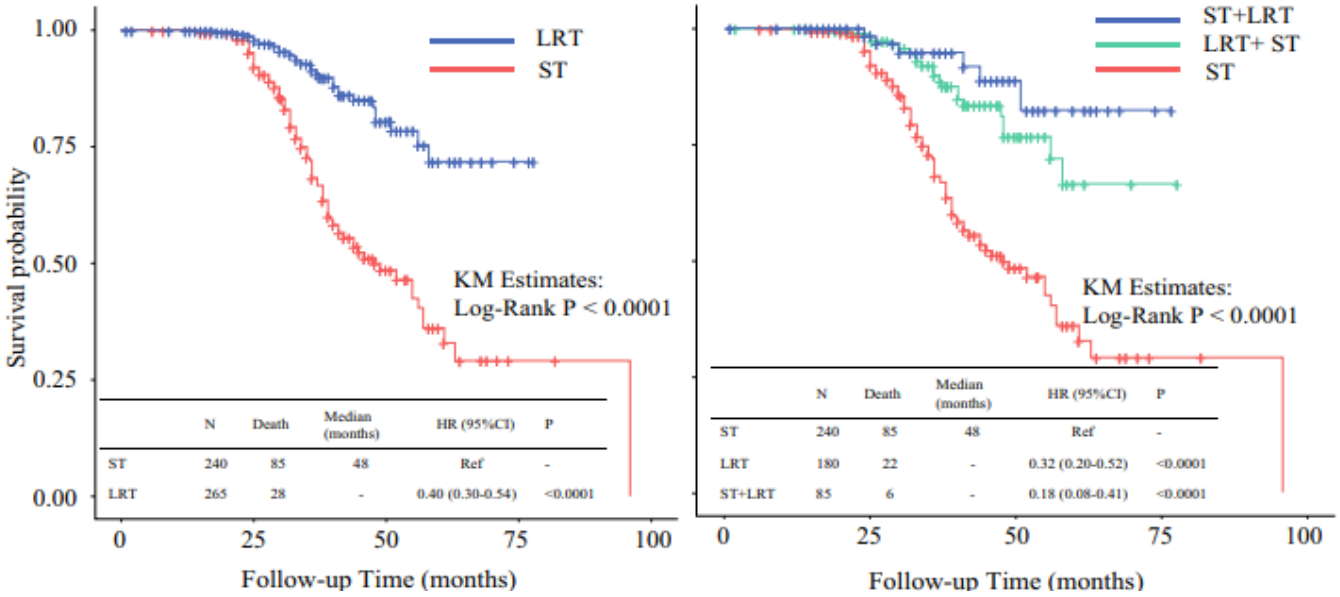
BOMET MF 14-01

- 505 patients prospective, multicenter registry study. Bone only metastasis.
- Five-year OS was 72% in the LRT group and 33% in the ST group
  - HR 0.40, 95% CI 0.30–0.54, p<0.0001
- Non-randomized study with clinicopathological differences in patients who underwent locoregional therapy.

		ST n:240 (%)	LRT n:265 (%)	*P*
Age (mean, years ± SD)		54.0±13.8	51.1±12.9	0.02
BMI (kg/m^2, mean ± SD)		28.3±4.5	27.8±4.5	0.21
Median follow-up (months)		33 (25–41)	34.9(24–45)	0.66
Tumor size	T1	28 (12)	48 (18)	0.0006
	T2	192 (80)	172 (65)	
	T3	20 (8)	45 (17)	
Grade	I	38 (16)	27 (10)	0.02
	II	95 (40)	135 (51)	
	III	107 (45)	103 (39)	
Histology	IDC	195 (81)	218 (82)	0.94
	ILC	20 (8)	20 (8)	
	Other	25 (10)	27 (10)	
ER/PR (+)		206 (86)	224 (85)	0.67
HER2/neu (+)		68 (28)	76 (29)	0.93
Triple negative		20 (8)	16 (6)	0.32
Bone metastasis number	Solitary	76 (32)	138 (52)	<0.000
	Oligometastases (< 4 metastases)	128 (53)	201 (76)	<0.000
	Multiple (≥ 4 metastases)	111 (46)	64 (24)	0.003
	> 5 metastases	64 (27)	41 (15)	0.002

BMI body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *ILC* invasive lobular carcinoma *IDC* invasive ductal carcinoma, *ST* systemic treatment, *LRT* locoregional treatment (ST+LRT an LRT+ST as LRT group)

Overall Survival (N=505)



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Soran et al, 2021

Takeaways

- Palliation of local symptoms is an indication for surgery in the metastatic setting.
- Overall randomized controlled trials do not show an overall survival advantage to local regional therapy in the setting of metastatic disease.
- There are certain cases for which surgery may be considered such as primary tumor progression with stable a distant disease and isolated contralateral metastasis. However a survival advantage has not been established.
  - These are difficult cases where patients must be considered on a case by case basis.
- Tumor board discussion and multidisciplinary consideration is important when considering surgery in the setting of metastatic disease.

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