Locoregional Treatment of the Primary Tumor in Patients with *De Novo* Stage IV Breast Cancer: a Radiation Oncologist's Perspective

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BACKGROUND

• ***De novo* stage IV breast cancer** which means metastatic disease from the start is diagnosed only in a small proportion of patients (less than 10%).

• Although the survival rate of stage IV breast cancer varies from months to years, most patients received only systemic therapy, and locoregional treatment (LRT) was done only for palliation purposes.

• The efficacy of LRT like surgery and/or radiotherapy (RT) is still controversial and several conflicting results have been reported in recent studies.

• In our retrospective study, we aim to assess the clinical outcomes of patients with *de novo* stage IV breast cancer after undergoing LRT of the primary site.

PATIENTS AND METHODS

• We retrospectively screened Yonsei University Health System's (two institution: Shinchon, Gangnam) database for patients who were firstly diagnosed with metastatic breast cancer and treated from January 2006 to November 2013.

→ Only patients who were initially diagnosed with distant metastasis at the first systemic evaluation were included.

→ **245 patients** (186 patient in Shinchon Severance and 59 patient in Gangnam Severance)

• "**LRT"** was defined as surgical resection and/or RT of the primary tumor site and/or axillary, internal mammary, supraclavicular lymph nodes.
- Only defined as the first case of local treatment, except for local treatment for symptom palliation after disease progression.
- The type and the timing of LRT were decided at the physician's discretion, in general in a multidisciplinary team setting.

• The use of systemic chemotherapy, hormone therapy or Human epidermal growth factor (HER2)-targeting therapy before/after LRT were also recored.

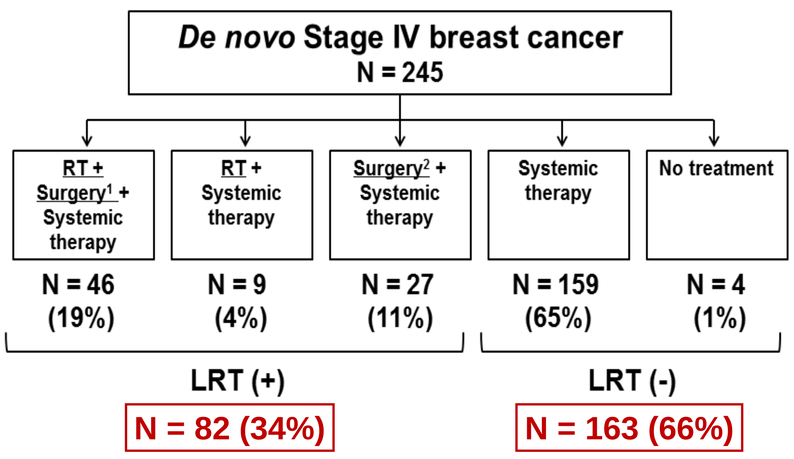


Figure 1. Treatment flowchart of all patients included in this study

- **Primary endpoint : local recurrence-free survival (LRFS)**
  - Local recurrence : recurrence in the breast, chest wall and/or regional LNs (axillary, supraclavicular)
  - Systemic recurrence : all other recurrences
- **Secondary endpoint : overall survival (OS)**

Table 1. Patients' characteristics

Characteristics	No.	%	Characteristics	No.	%
Age (year)	Median 50 (range, 26-80)		No. of metastatic sites		
<50	118	48	<5	86	35
≥50	127	52	≥5	159	65
T stage			ER status		
Tis	1	0	Positive	158	65
T1	25	10	Negative	83	34
T2	95	39	Unknown	4	2
T3	32	13	PR status		
T4	87	36	Positive	110	45
Tx	5	2	Negative	131	53
N stage			Unknown	4	2
N0	23	9	HER2 status		
N1	45	18	Positive	88	36
N2	70	29	Negative	152	62
N3	105	43	Unknown	5	2
Nx	2	1	Ki-67 LI status		
Metastatic site			High	68	28
Bone	167	68	Low	87	35
Lung	84	34	Unknown	90	37
Liver	59	24	Hormone therapy		
Visceral organ	5	2	Yes	110	45
Distant LN	72	29	No	135	55
Brain	13	5	Chemotherapy		
Soft tissue	1	0	Yes	220	90
			No	25	10

• From the first diagnosis, LRT was performed on median 5.2 months (range, 0-61.3 months).

• RT dose : median 50.4 Gy (range, 21.6-60.4 Gy)

• RT field :
- Whole breast only 9 (16%) (3 in BCS + RT group, 1 in MRM + RT group, 5 in RT alone group) regardless of N stage
- Regional LNs area 46 (84%) (6 in BCS + RT group, 36 in MRM + RT group, 4 in RT alone group)

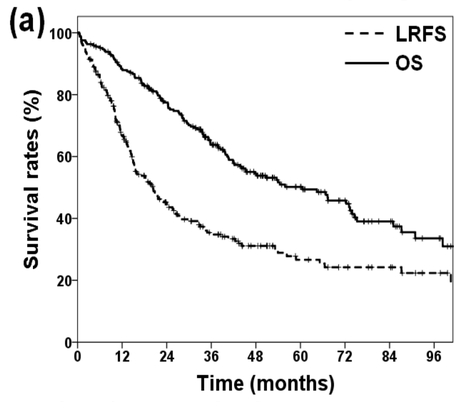
• Surgery type: mastectomy 88% (N = 64), BCS 12% (N = 9)

• 63/82 (77%) had neoadjuvant chemotherapy before the start of LRT and 52 (83%) showed responses after chemotherapy.

RESULTS

1) Survival outcomes and prognostic factors

• **Median f/u : 40 months (range, 13 days-124 months)**



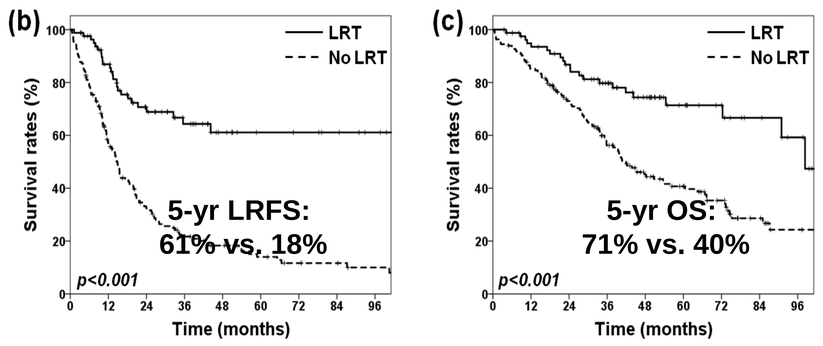
• **LRFS : median 20 months, 3-yr 35%, 5-yr 27%**
• **OS : median 61 months, 3-yr 64%, 5-yr 50%**

• **Total recurrences : 188 (77%)**
- **local recurrence : 45%**
(LRT group 12% vs. No LRT group 49%, p <0.001)
- **systemic recurrence : 95%**
(LRT group 69% vs. No LRT group 76%, p = 0.19)

• **Univariate analysis :**
- LRFS : advanced T stage (T4), liver or brain metastasis, ≥5 metastatic sites, hormone therapy, LRT
- OS : advanced T stage (T4), liver or brain metastasis, hormone therapy, LRT , response to neoadjuvant chemotherapy

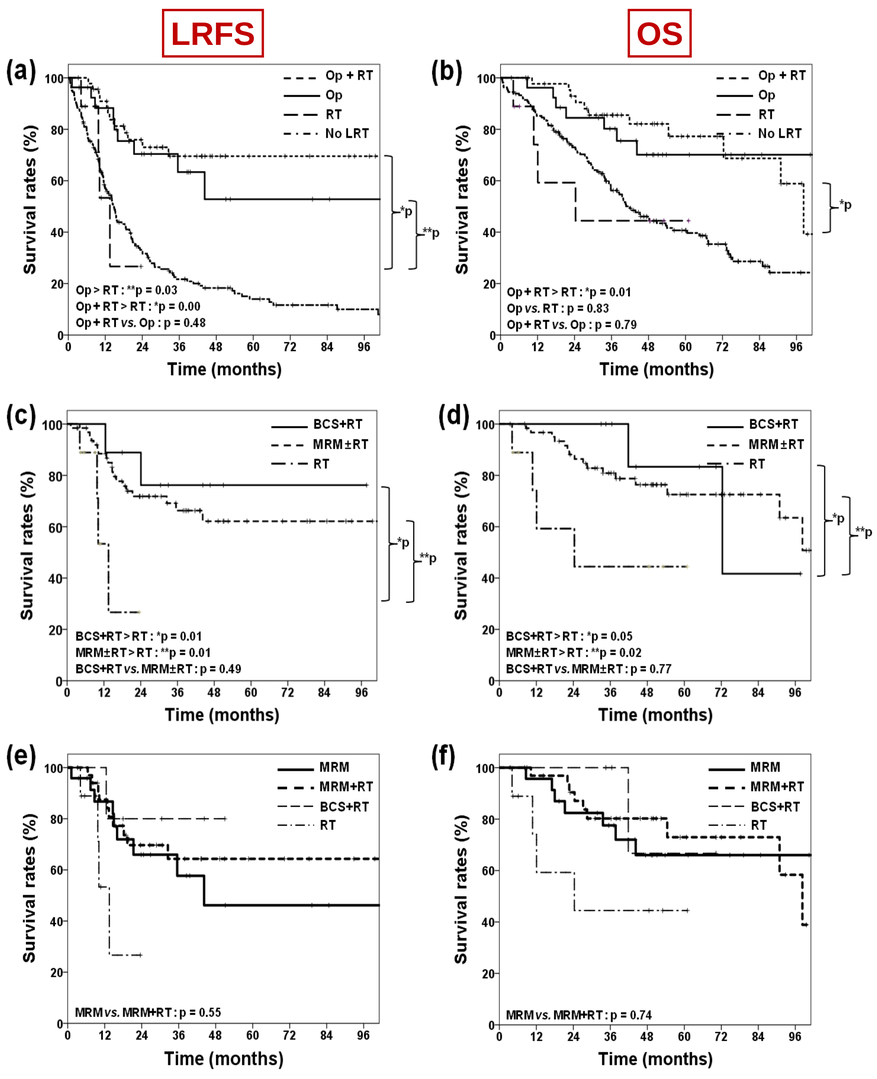
• **Multivariate analysis**
- LRFS : advanced T stage (T4), liver or brain metastasis, ≥5 metastatic sites, hormone therapy, surgery
- OS : advanced T stage (T4), hormone therapy

2) LRT group versus No LRT group



LRT group : *more favorable ?*

• Liver metastasis ↓ (14% vs. 30%, p = 0.01),
• Brain metastasis ↓ (0% vs. 8%, p = 0.01),
• <5 metastatic sites ↑ (52% vs. 26%, p <0.001),
• Patients receiving hormone therapy ↑ (56% vs. 39%, p = 0.01)



• Even after matching the baseline characteristics by propensity score matching method, survival rates were still significantly higher in LRT group than no LRT group (5-yr LRFS 55% vs. 22%, p <0.001, 5-yr OS 71% vs. 43%, p <0.001).

BCS+RT vs. MRM±RT

• MRM ± RT group and BCS + RT group were better than RT only group, however, BCS+RT group showed better outcome than MRM±RT group (5-yr LRFS 76% vs. 62%, p = 0.05, 5-yr OS 82% vs. 71%, p = 0.77)

MRM vs. MRM+RT

In tumors of advanced stage (≥N2, ≥T3, or T2N1) (N = 72),

• Treatment results were similar or better in MRM+RT group (N = 34) than MRM only group (N = 24) although there was no statistical difference (5-yr LRFS MRM+RT 64%, MRM 46%, p = 0.55; 5-yr OS MRM+RT 73%, MRM 66%, p = 0.74; 5-yr local-recurrence rate MRM+RT 19%, MRM 22%)

CONCLUSION

• Our data confirms that upfront LRT including RT is an important option together with systemic therapies in *de novo* stage IV breast cancer patients, especially when the burden of tumor is low.

• BCS + RT would be a possible substitute for MRM without compromising oncologic outcome in early stage metastatic breast cancer.

• For the role of post-mastectomy RT, outcomes might be higher with RT in selected patients (≥N2, ≥T3, or T2N1). Post-mastectomy RT should be re-evaluated in a modern era in which systemic treatment developed, with improving survival in stage IV disease.

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