GBCC2018

Clinicopathological Factors Affecting Distant Metastasis Following Loco-Regional Recurrence of breast cancer

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Cheol Min Kang

Department of surgery, University of Ulsan Collage of Medicine
Breast Cancer Center, Asan Cancer Institute, Seoul, Korea

- **Local or regional recurrence (LRR)**

  - associated with poor prognosis

  - substantial risk of developing subsequent distant metastasis (DM)

Taghian A, et al, Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. 2004, J Clin Oncol 22:4247-4254

Wapnir IL, et al, Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. 2006, J Clin Oncol 24:2028-2037

Stewart J. Anderson, et al, Prognosis After Ipsilateral Breast Tumor Recurrence and Locoregional Recurrences in Patients Treated by Breast-Conserving Therapy in Five National Surgical Adjuvant Breast and Bowel Project Protocols of Node-Negative Breast Cancer, 2009, J Clin Oncol 27:2466-2473
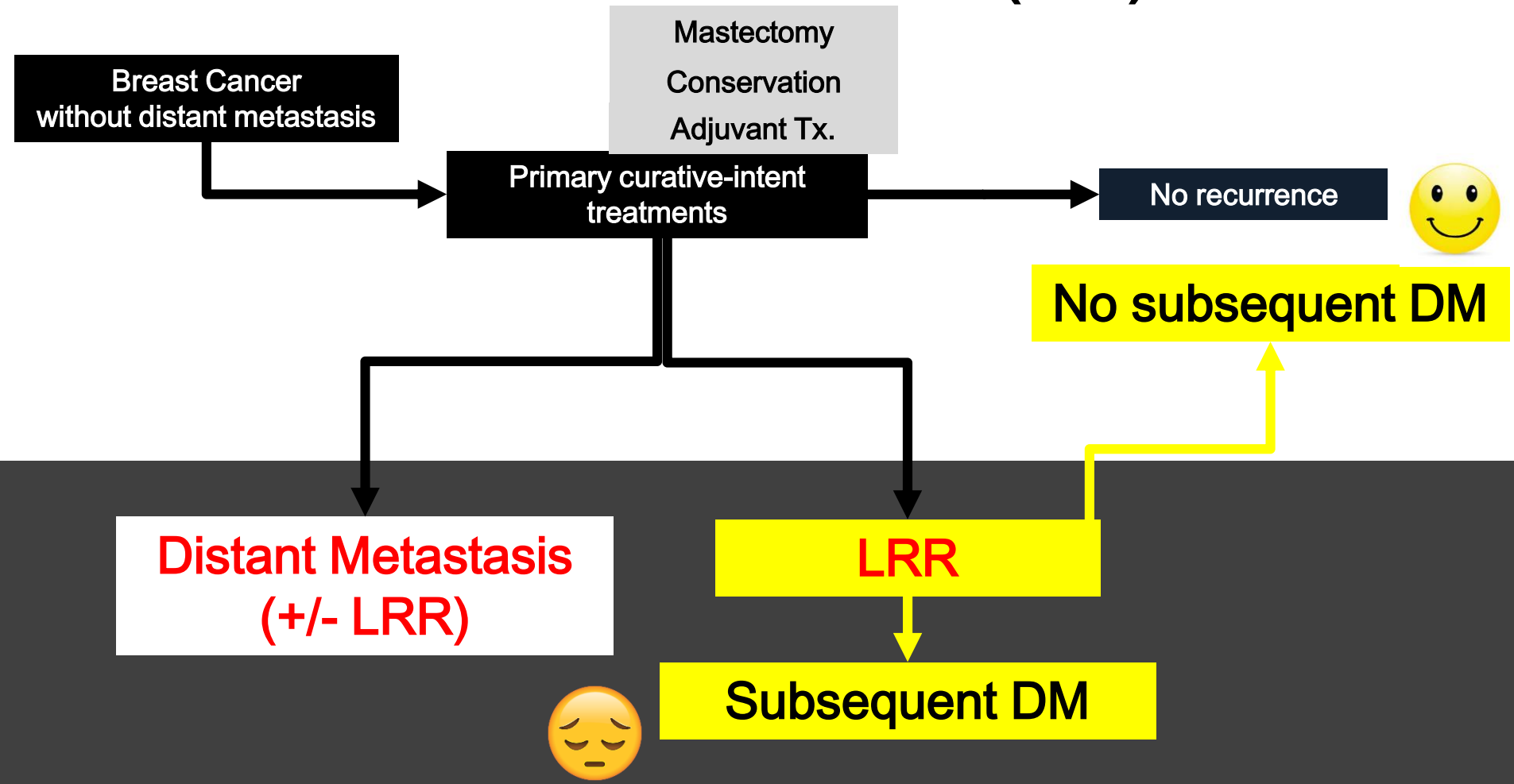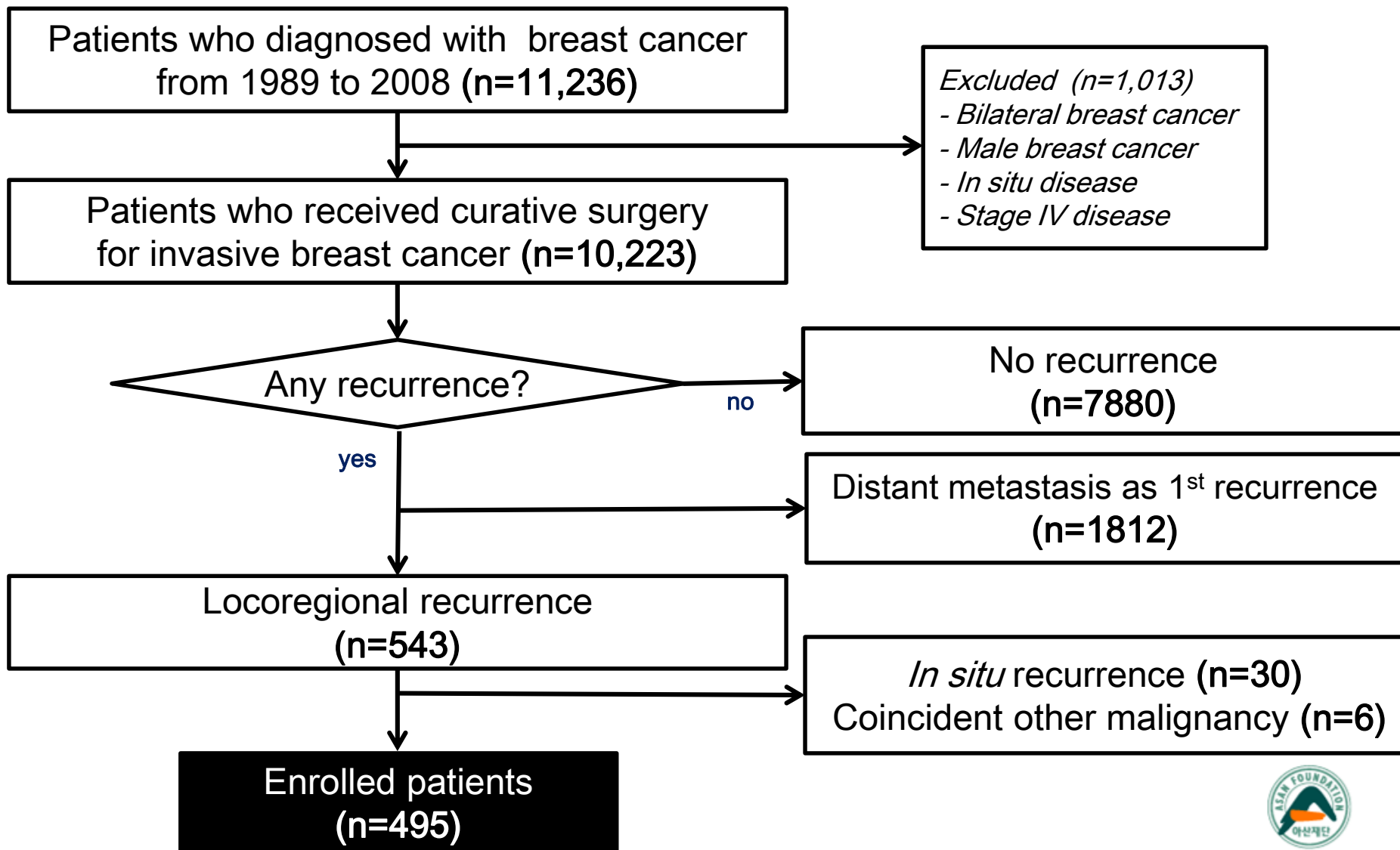
To investigate clinicopathological factors associated with subsequent DM in breast cancer patients with <u>LRR as a first event</u>

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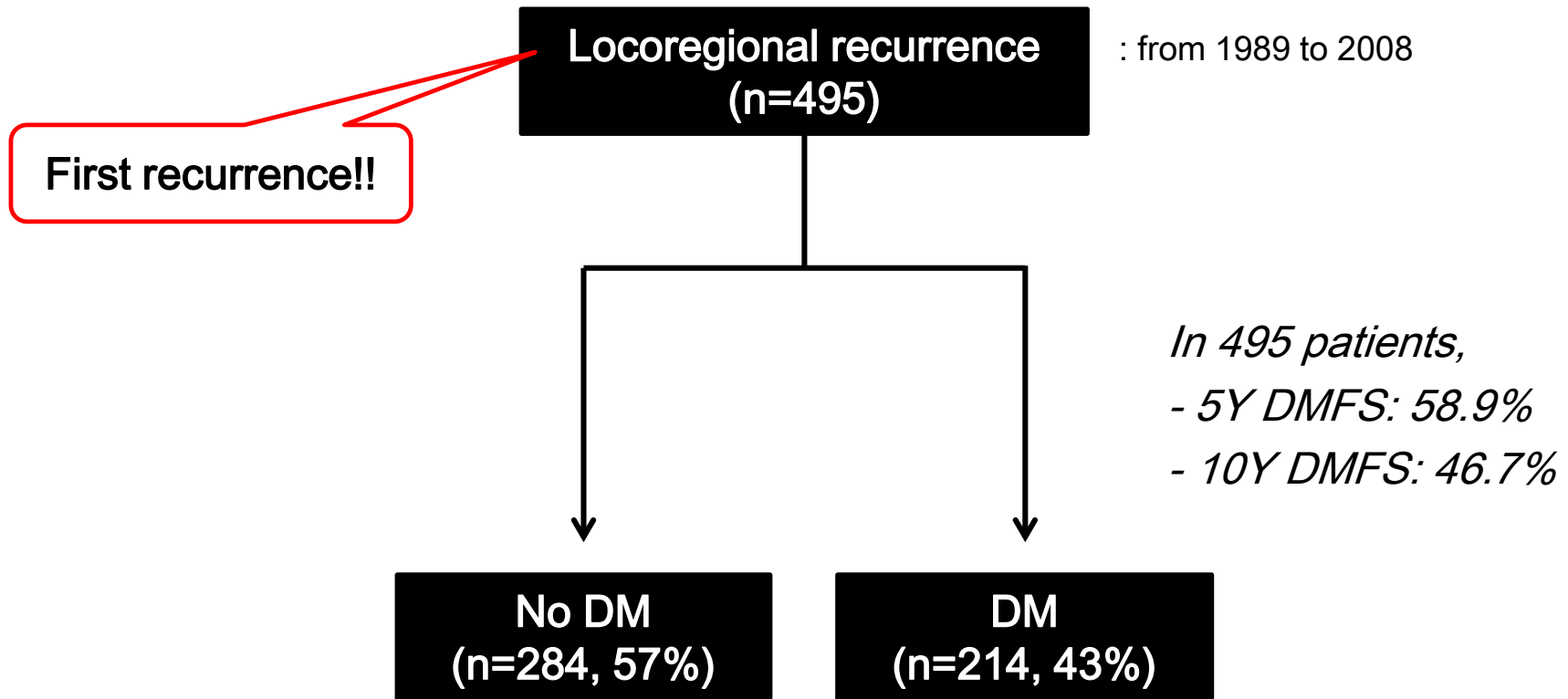Asan Medical Center

Patients & Methods

Median F/U period since curative surgery = 114.2mo (1.0~230.6)

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Patients who diagnosed with breast cancer
from 1989 to 2008 (n=11,236)
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→
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Excluded (n=1,013)
- Bilateral breast cancer
- Male breast cancer
- In situ disease
- Stage IV disease
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Patients who received curative surgery
for invasive breast cancer (n=10,223)
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Any recurrence? — no →
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No recurrence
(n=7880)
```

yes

→
```
Distant metastasis as 1st recurrence
(n=1812)
```

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Locoregional recurrence
(n=543)
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→
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In situ recurrence (n=30)
Coincident other malignancy (n=6)
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Enrolled patients
(n=495)
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Median F/U period since LRR = 65mo (1.0~249)

Locoregional recurrence (n=495) : from 1989 to 2008

First recurrence!!

In 495 patients,
- *5Y DMFS: 58.9%*
- *10Y DMFS: 46.7%*

No DM (n=284, 57%)

DM (n=214, 43%)

Disease free interval (DFI) < 30mo: 47%
Local recurrence: 50%, Regional recurrence: 50%

Table 1. Characteristics of 495 patients with locoregional recurrence

Characteristics	No.	%	Characteristics	No.	%	Characteristics	No.	%
Age at diagnosis(year)			Stage			Adjuvant radiotherapy		
<35	84	17.0	I	153	30.9	Yes	239	49.2
≥35	411	83.0	II	228	46.1	No	247	50.8
Type of surgery			III	114	23.0	Unknown	9	
Mastectomy	296	59.8	Estrogen receptor			Adjuvant hormone therapy		
BCS	199	40.2	Negative	223	46.9	Yes	304	63.3
Histologic grade			Positive	252	53.1	No	176	36.7
G1-2	210	51.1	Unknown	20		Unknown	15	
G3	201	48.9	Progesterone receptor			DFI(months)		
Unknown	84		Negative	245	52.1	<30	231	46.7
Nuclear grade			Positive	225	47.9	≥30	264	53.3
G1-2	184	51.4	Unknown	25		Type of recurrence		
G3	174	48.6	HER2			Local	245	49.5
Unknown	137		Negative	207	64.9	Regional	250	50.5
Lymphovascular invasion			Positive	112	35.1	*Local treatment after recurrence		
Yes	123	43.2	Unknown	176		Surgery only	182	40.6
No	162	56.8	Subtype			Radiotherapy only	39	8.7
Unknown	210		HR+/HER2-	125	39.2	Surgery and radiotherapy	195	43.5
Tumor size(cm)			HR+/HER2+	49	15.4	None	32	7.1
≤2	230	46.5	HR-/HER2+	63	19.7	Unknown	47	
>2	265	53.5	TNBC	82	25.7	Chemotherapy after recurrence		
Lymph node			Unknown	176		Yes	105	23.3
Negative	234	47.3	Adjuvant chemotherapy			No	346	76.7
Positive	161	52.5	Yes	349	71.2	Unknown	44	
			No	141	28.8			
			Unknown	5				

BCS: breast conserving surgery, HER2: human epidermal growth factor 2, HR: hormone receptor, TNBC: triple negative breast cancer, DFI: disease free survival
*Local treatment after recurrence contains surgery and radiotherapy.

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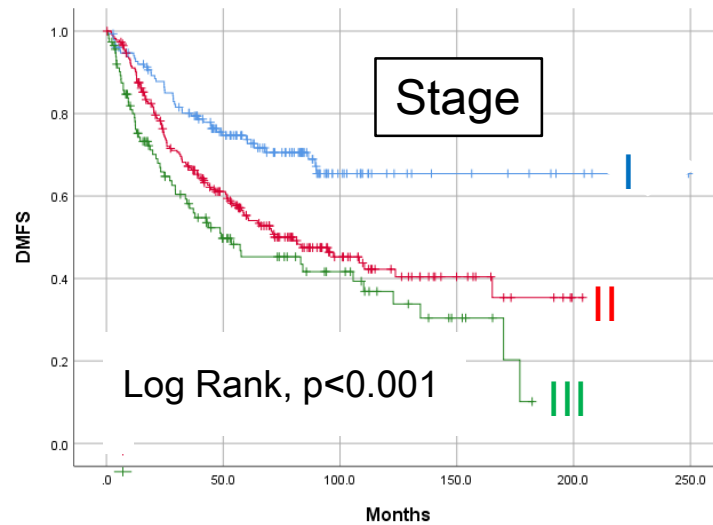## Mastectomy, LVI(+), larger tumor size (>2cm) and LN(+) "at diagnosis"

Table 2. Clinicopathological factors associated with distant metastasis in locoregional recurrence

Characteristics	Distant metastasis following LRR No.(%)		P-value
	(-) 284(46.8)	(+) 214(43.2)	
Age(year)			0.106
<35	41(48.8)	43(51.2)	
≥35	240(58.4)	171(41.6)	
Type of primary surgery			0.003
Mastectomy	152(51.4)	144(48.6)	
BCS	129(64.8)	70(35.2)	
Histologic grade			0.092
G1-2	108(51.4)	102(48.6)	
G3	120(59.7)	81(40.3)	
Nuclear grade			0.856
G1-2	104(56.5)	80(43.5)	
G3	100(57.5)	74(42.5)	
Lymphovascular invasion			<0.001
No	107(66.0)	55(34.0)	
Yes	54(43.9)	69(56.1)	
Tumor size(cm)			0.005
≤2	146(63.5)	84(36.5)	
>2	135(50.9)	130(49.1)	
Lymph node			<0.001
Negative	162(69.2)	72(30.8)	
Positive	119(45.6)	142(54.4)	
Stage			<0.001
I	110(71.9)	43(28.1)	
II	118(51.8)	110(48.2)	
III	53(46.5)	61(53.5)	
Estrogen receptor			0.607
Negative	130(58.3)	93(41.7)	
Positive	141(56.0)	111(44.0)	

LN: lymph node, BCS: breast conserving surgery

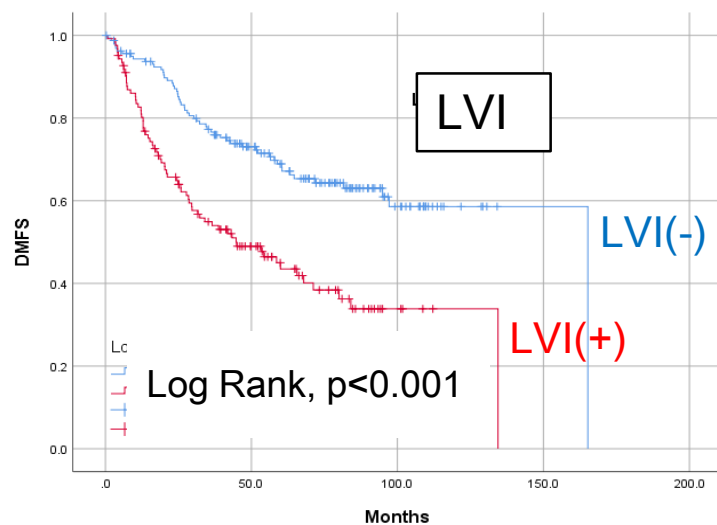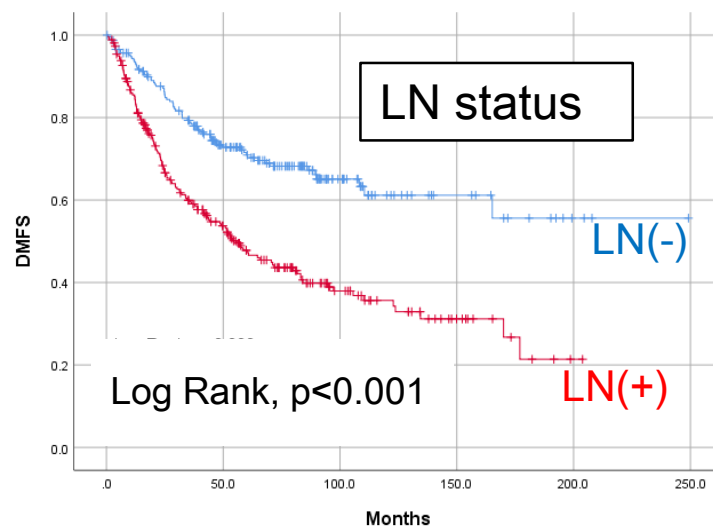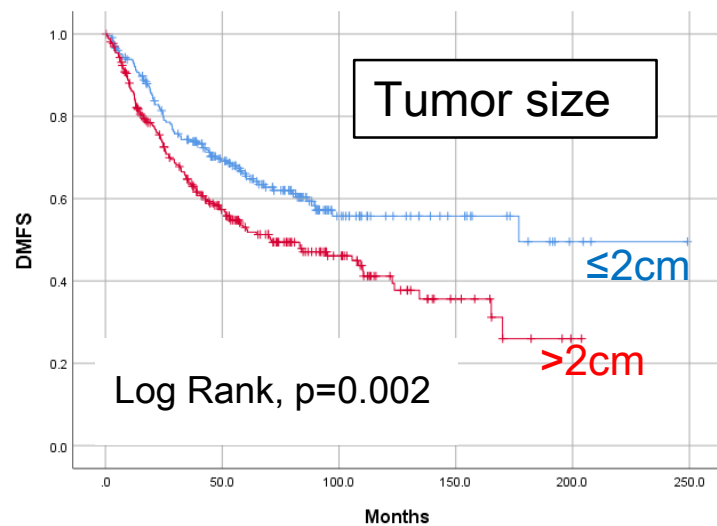**Shorter DFI (<30m) and LN(+) "at recurrence"**

Table 2. Clinicopathological factors associated with distant metastasis in locoregional recurrence (continued)

Characteristics	Distant metastasis following LRR No.(%)		P-value
	(-) 284(46.8)	(+) 214(43.2)	
Progesterone receptor			0.684
Negative	137(55.9)	108(44.1)	
Positive	130(57.8)	95(42.2)	
HER2			0.672
Negative	127(61.4)	80(38.6)	
Positive	66(58.9)	46(41.1)	
Subtype			0.979
HR+/HER2-	77(61.6)	48(38.4)	
HR+/HER2+	29(59.2)	20(40.8)	
HR-/HER2+	37(58.7)	26(41.3)	
TNBC	50(61.0)	32(39.0)	
Adjuvant chemotherapy			**0.006**
Yes	185(53.0)	164(47.0)	
No	94(66.7)	47(33.3)	
Adjuvant radiotherapy			0.488
Yes	140(58.6)	99(41.4)	
No	137(55.5)	110(44.5)	
Adjuvant hormone therapy			0.651
Yes	174(57.2)	130(42.8)	
No	97(55.1)	79(44.9)	
DFI(months)			**0.001**
<30	112(48.5)	119(51.5)	
≥30	169(64.0)	95(36.0)	
Type of recurrence			**0.002**
Local	156(63.7)	89(36.3)	
Regional	125(50.0)	125(50.0)	
Local treatment after recurrence			0.647
Yes	244(55.2)	198(44.8)	
No	19(59.4)	13(40.6)	
Chemotherapy after recurrence			0.776
Yes	56(57.3)	49(47.7)	
No	190(54.9)	156(45.1)	

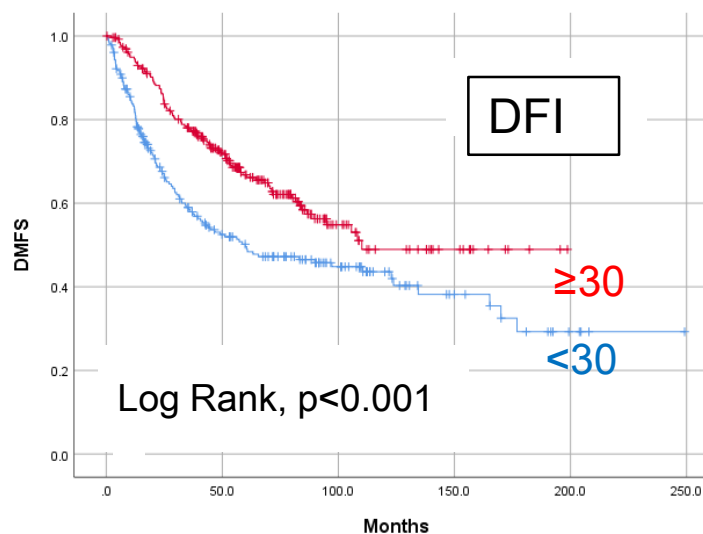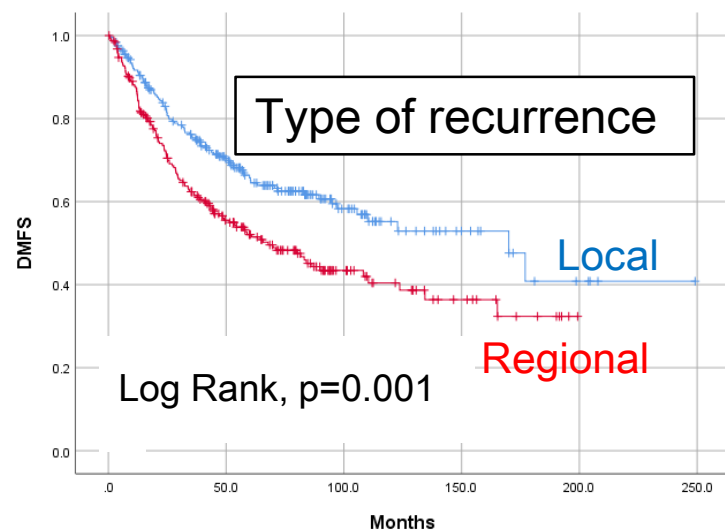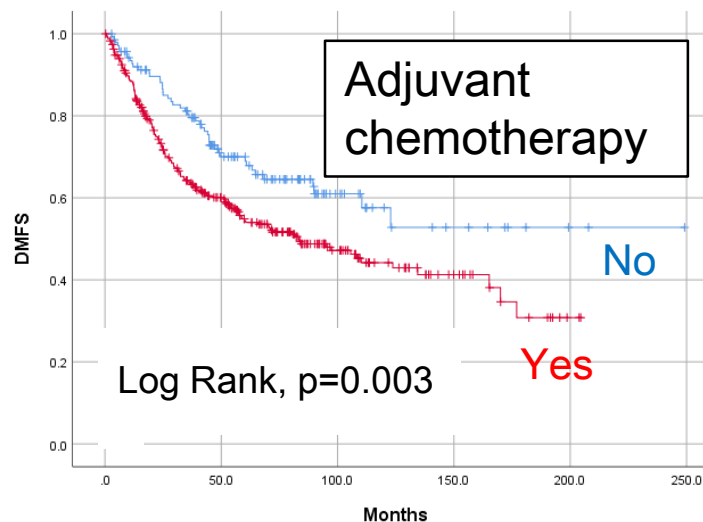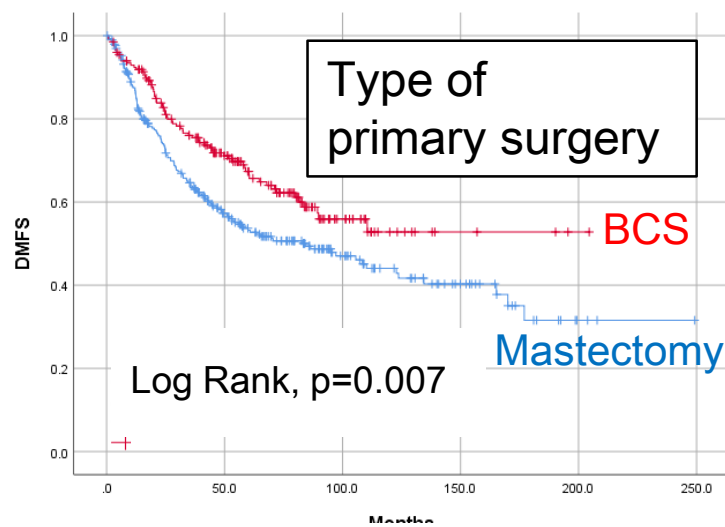HER2: human epidermal growth factor 2, TNBC: triple negative breast cancer, DFI: disease free interval

Figure 1. Kaplan-Meier analysis of distant metastasis-free survival in LRR

Figure 1. Kaplan-Meier analysis of distant metastasis-free survival in LRR (continued)

Type of primary surgery

BCS

Mastectomy

Log Rank, p=0.007

Adjuvant chemotherapy

No

Yes

Log Rank, p=0.003

Type of recurrence

Local

Regional

Log Rank, p=0.001

DFI

≥30

<30

Log Rank, p<0.001

Independent predictor for subsequent DM
LN(+) at Diagnosis, Shorter DFI, and LN(+) at LRR

Table 3. Factors associated distant metastasis and survival in locoregional recurrence

variable	DMFS		BCSS		OS	
	p-value	HR(95% CI)	p-value	HR(95% CI)	p-value	HR(95% CI)
Age(<34yrs vs ≥35yrs)	0.037	1.49(1.02~2.15)	0.298	1.23(0.84~1.80)	0.322	1.21(0.83~1.76)
Type of surgery(mastectomy vs BCS)	0.905	0.98(0.71~1.35)	0.239	0.82(0.58~1.15)	0.166	0.80(0.58~1.10)
Tumor size(>2cm vs ≤2cm)	0.396	1.14(0.84~1.55)	0.207	1.22(0.90~1.67)	0.137	1.26(0.93~1.69)
LN status(positive vs negative)	<0.001	2.07(1.47~2.91)	<0.001	2.31(1.61~3.30)	<0.001	2.22(1.57~3.13)
ER(negative vs positive)	0.560	1.10(0.81~1.49)	0.028	1.43(1.04~1.98)	0.006	1.55(1.14~2.12)
Adjuvant chemotherapy(yes vs no)	0.912	1.02(0.70~1.50)	0.955	0.99(0.66~1.47)	0.336	0.83(0.57~1.21)
DFI(≤30mo vs >30mo)	0.002	1.61(1.19~2.17)	<0.001	1.92(1.40~2.64)	<0.001	1.81(1.34~2.45)
Type of recurrence(regional vs local)	0.003	1.59(1.17~2.16)	0.017	1.47(1.07~2.02)	0.019	1.44(1.06~1.95)
*Local treatment after LRR(yes vs no)	0.721	1.12(0.61~2.04)	0.003	0.51(0.33~0.79)	0.002	0.50(0.32~0.77)
Chemotherapy after LRR(no vs yes)	0.857	0.97(0.67~1.39)	0.047	1.43(1.01~2.05)	0.139	1.30(0.92~1.85)

BCS: breast conserving surgery, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, DFI: disease free survival, DMFS: distant metastasis free survival, BCSS: breast cancer specific survival, OS: overall survival, HR: hazard ratio, CI: confidence interval
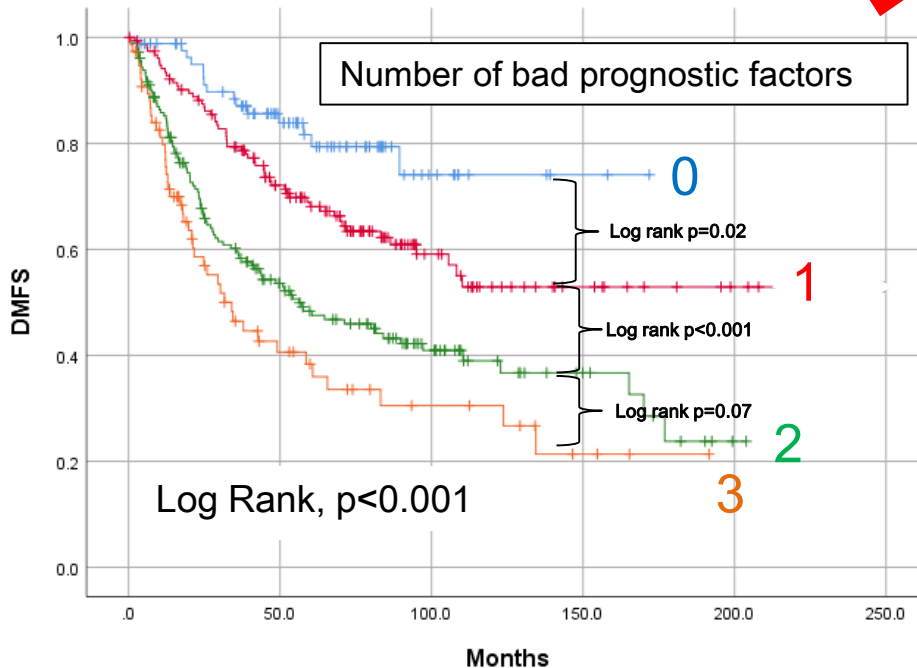*Local treatment after LRR contains surgery and radiotherapy.

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Discussion

- ## Practical application of the results
  : Risk subgrouping by the number of bad prognostic factors

Figure 2. Kaplan-Meier analysis of distant metastasis-free survival by number of bad prognostic factors

good	Prognostic factor	bad
negative	LN status at diagnosis	positive
≥30mo	DFI	<30mo
no	Regional recurrence	yes

*Adjustment by age at diagnosis, type of primary surgery, initial tumor size, estrogen receptor, adjuvant chemotherapy, chemotherapy after LRR, and local treatment after LRR

Number of bad prognostic factors	5Y DMFS(%)	*Adjusted HR	5Y BCSS(%)	*Adjusted HR	5Y OS(%)	*Adjusted HR	no.
0	79.4	Reference	87.8	Reference	85.2	Reference	84(17.0%)
1	68.1	1.60 (0.89~2.96)	83.0	1.39(0.69~2.83)	81.7	1.37(0.72~2.63)	156(31.5%)
2	47.6	3.23 (1.80~5.79)	55.8	3.24(1.66~6.35)	55.1	2.92(1.57~5.43)	179(36.2%)
3	36.0	4.65 (2.40~9.01)	35.5	5.22(2.52~10.8)	32.9	4.75(2.41~9.37)	76(15.4%)
Total	59.9		66.4		64.6		495

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- ## Comparison with previous studies

Organization		SMC*	SNU†	Present study (AMC)
Follow up period		January,2000~December,2010	January,1995~December,2010	July,1989~December,2008
Median follow up period		106.8mo	71mo(6~229)	114.2m(1.0~230.6)
No. of patients		104	208	495
Median age at diagnosis		46y(27~76)	46y(21~77)	44y(21~81)
Type of surgery	BCO	61(59%)	95(46%)	119(40%)
	Mastectomy	43(41%)	113(54%)	256(60%)
Type of recurrence	Local	69(66%)	117(56%)	245(50%)
	Regional	35(34%)	90(44%)	250(50%)
Median DFS		35.7mo(4.5~132.3)	30mo(1~204)	32.1mo(1.0~230.6)
Median DMFS		66mo	23mo(0~167)	47.1mo(1.0~209.5)
5Y DMFS		54%	Not described	58.9%
Significant factors with DM in univariate analysis		Not described	Type of primary surgery, Tumor size, LN status, Adjuvant chemotherapy, Type of recurrence, DFI	Type of primary surgery, Tumor size, LN status, stage, LVI, Adjuvant chemotherapy, Type of recurrence, DFI
Significant factors with DM in multivariate analysis		Age, stage, TNBC, DFI_24 Type of recurrence	DFI_30	Age, LN status, DFI_30, Type of recurrence

BCS: breast conserving surgery, DM: distant metastasis, DFS: disease free survival, DFI: disease free interval, LN: lymph node, LVI: lymphovascular invasion

* Soojin Park, et al, Risk Factors Associated with Distant Metastasis and Survival Outcomes in Breast Cancer Patients with Locoregional Recurrence, J Breast Cancer. 2015 Jun;18(2):160-166
† Min-Young Lee, Clinicopathological Features and Prognostic Factors Affecting Survival Outcomes in Isolated Locoregional Recurrence of Breast Cancer: Single-Institutional Series, 2016, PLoS ONE 11(9): e0163254. doi:10.1371/journal. pone.0163254

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- ## ER negativity
  : Not predictor for subsequent DM, but prognosticator for BC specific death

- Visceral metastasis shows worse prognosis than bone metastasis and ER negativity is relatively high.
- Within the same organ, the ER negative group has worse prognosis.

* Figure 2: The frequencies of the sites of distant metastasis by breast cancer subtypes.

†5Y OS after the time of diagnosis

Bone(s)

Bone(m)

visceral
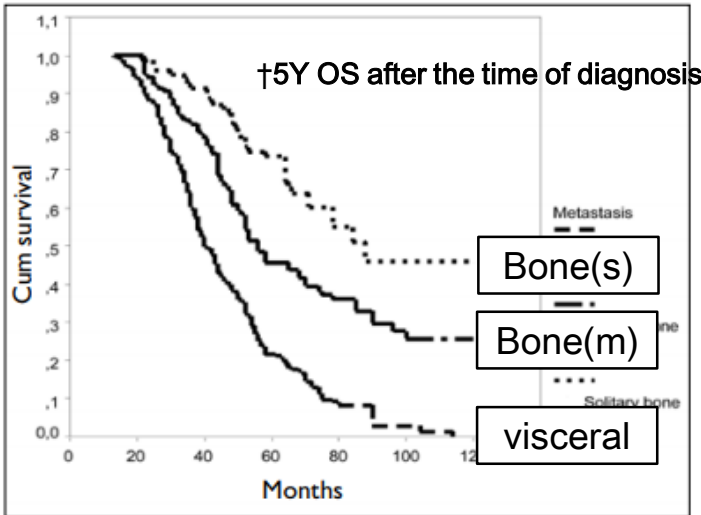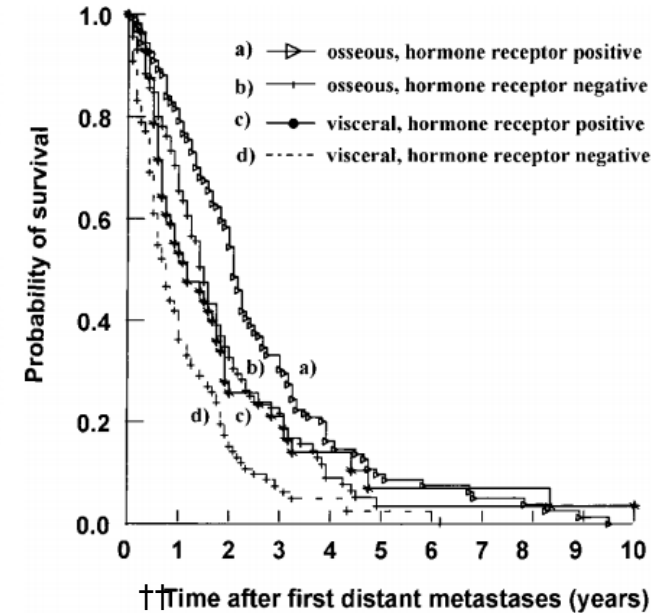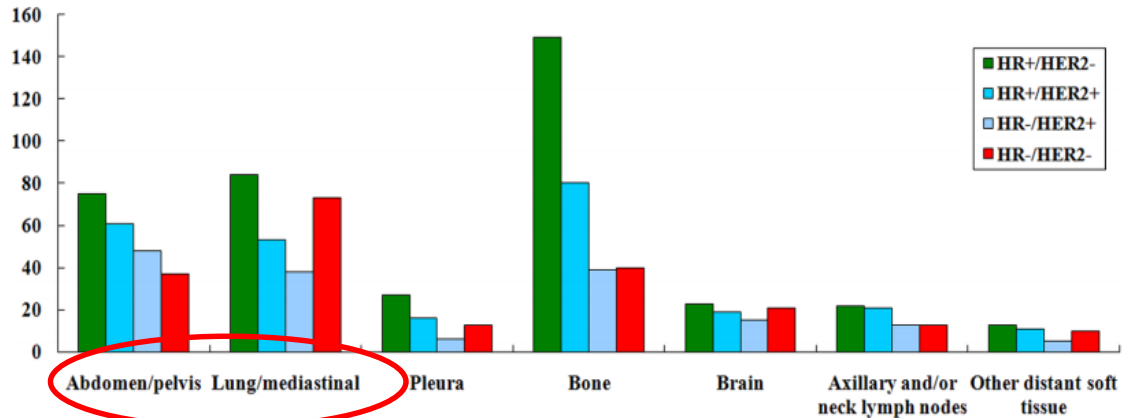
* San-Gang Wu, et al, Patterns of distant metastasis in Chinese women according to breast cancer subtypes, 2015, Oncotarget, Vol.7, No.30
† Kuru B, et al, Prognostic factors for survival in breast cancer patients who developed distant metastasis subsequent to definitive surgery, 2008, Singapore Med J, 49(11) 904~911
†† E.-F. Solomayer, et al, Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis, 2000, Breast Cancer Res Treat 59(3):271~278

†† Time after first distant metastases (years)

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1. Ipsilateral breast tumor recurrence (IBTR) in women with breast cancer treated with BCS was not classified as 'true recurrence (TR)' or 'new primary (NP)' in this retrospective analysis. Exact discrimination between TR and NP will require standardized pathology and molecular analyses in the prospective setting.

2. Data on various patterns of subsequent DM were not included in this analysis. Addressing this issue in future studies could provide more sophisticated metastasis site-specific predictors.

3. The effect of local and systemic treatment modalities for isolated LRR on survival outcome was not the scope of this study. Addressing this issue for the higher risk subjects with potential systemic involvement would help individualize retreatment by the expected risk-benefit ratio.

1. LN(+) at diagnosis, shorter DFI, and LN involvement (+)at recurrence were independent predictors for subsequent DM following isolated LRR of breast cancer.

2. ER negativity was a less favorable prognosticator for BCSS and OS, but not a predictor for subsequent DM, which can be caused by more devastating dissemination of subsequent DM events.

3. Subsequent DM risk-based subgrouping using these predictors for the patients with isolated LRR can be practically used when the physicians and the patients make shared decision in the real oncology clinic.

Thank you for your attention!

2018/04/05 Cheol Min Kang

Predicting distant metastasis after locoregional recurrence