GBCC2019 Global Breast Cancer Conference 2019
April 25 (Thu) - 27 (Sat), 2019
Songdo ConvensiA, Incheon, Korea

Radiation Oncologist's View for Escalation or De-escalation

Mi Young Kim

DEPARTMENT OF RADIATION ONCOLOGY
KYUNGPOOK NATIONAL UNIVERSITY CHILGOK HOSPITAL

Radiation Oncology view for

- Escalation

→ Mastectomy : PMRT

→ Breast conserving surgery : Breast + Regional lymph node RT

→ Radiation dose escalation, radiosensitizer…..

- De-escalation

→ Mastectomy : omission of PMRT

→ Breast conserving surgery : Breast RT only

Radiation Oncology view for

- **Escalation**

→ **Mastectomy : PMRT**

→ Breast conserving surgery : Breast + Regional lymph node RT

→ Radiation dose escalation, radiosensitizer…..

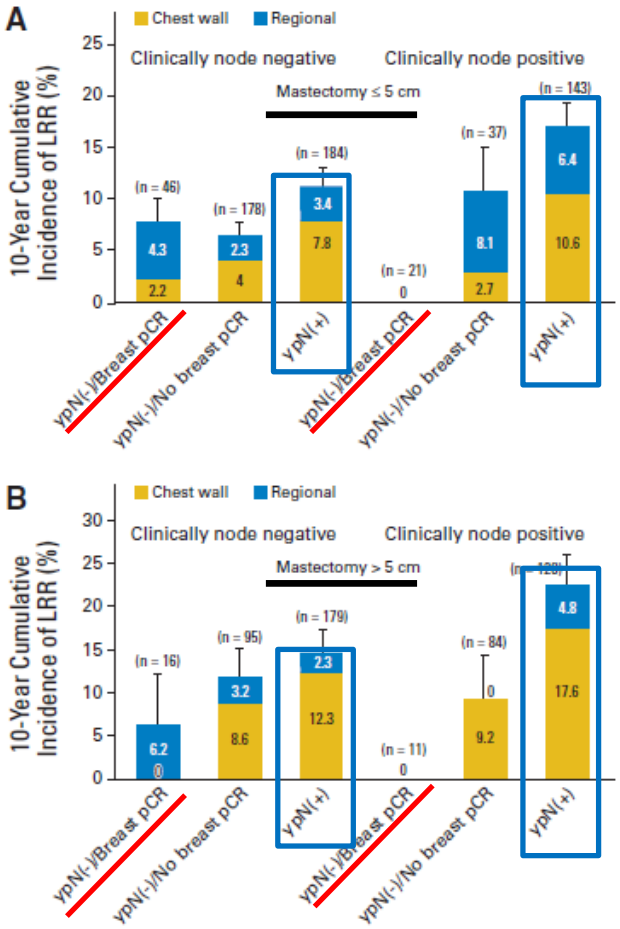
- **De-escalation**

→ **Mastectomy : omission of PMRT**

→ Breast conserving surgery : Breast RT only

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

- NAC → BCS+ Breast RT (no RNI) / **Mastectomy + no RT**



10- year LRR; 8.9% (local), 3.4%(regional)

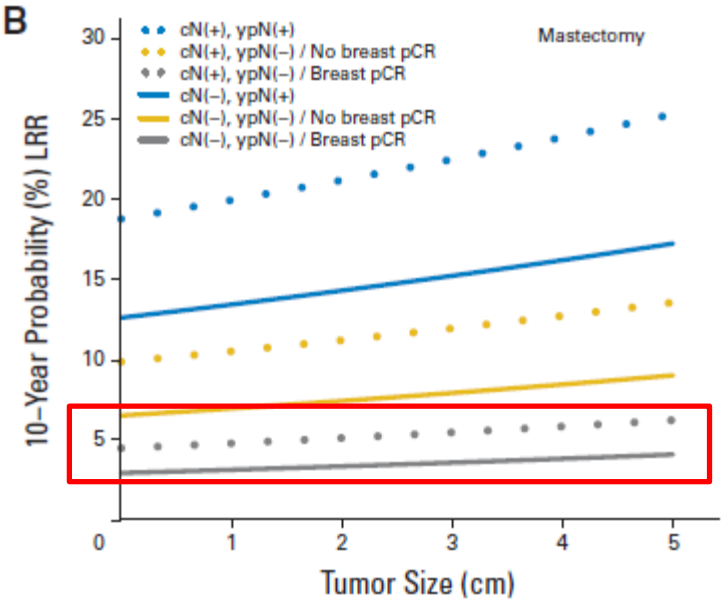
JCO 2012;30:3960-3966

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

Table 2. Multivariate Analysis of Independent Predictors of 10-Year LRR in the Combined Data Set*

Variable	HR	95% CI	P
Age ≥ 50 *v* < 50 years†	0.78	0.63 to 0.98	.03
Clinical tumor size > 5 *v* ≤ 5 cm†	1.51	1.19 to 1.91	< .001
Clinical nodal status cN(+) *v* cN(−)†	1.61	1.28 to 2.02	< .001
Nodal/breast pathologic status			< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†	1.55	1.01 to 2.39	
ypN(+) *v* ypN(−)/breast pCR†	2.71	1.79 to 4.09	

Age, clinical tumor size, clinical nodal status, pathologic nodal/ breast status
→ LRR

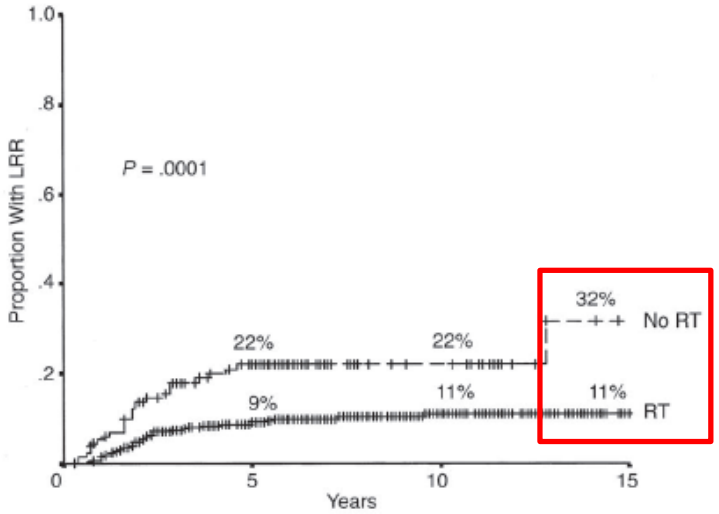


ypCR (breast ypCR, ypN(-))
→ LRR rate low

JCO 2012;30:3960-3966

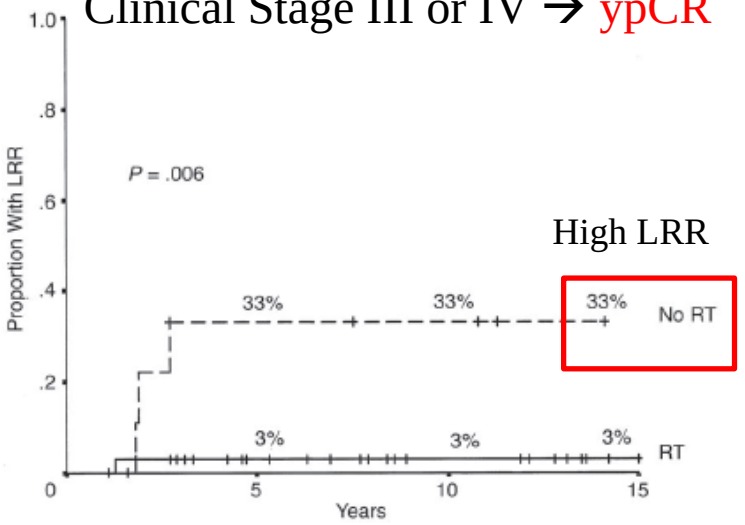
Postmastectomy Radiation Improves Local-Regional Control and Survival for Selected Patients With Locally Advanced Breast Cancer Treated With Neoadjuvant Chemotherapy and Mastectomy

- NAC+ mastectomy+ PMRT ; 542 patients
- NAC+ mastectomy ; 134 patients



	No. Patients	No. Events
No RT	134	28
RT	542	50

Clinical Stage III or IV → ypCR



	No. Patients	No. Events
No RT	11	3
RT	35	1

JCO 2004;22:4691-4699

Postmastectomy Radiation Improves Local-Regional Control and Survival for Selected Patients With Locally Advanced Breast Cancer Treated With Neoadjuvant Chemotherapy and Mastectomy

Table 5. Ten-Year Actuarial Rates of CSS According to Clinical and Pathological Disease Status

Factor	10-Year CSS Rate		*P*
	No Radiation (%)	Radiation (%)	
Combined clinical stage			
I-II	73	71	.482
IIIA	64	70	.742
≥ IIIB	22	44	.002
Clinical T-stage			
T1	80	92	.550
T2	56	66	.977
T3	71	69	.878
T4	24	45	.007
Clinical N-stage			
N0	65	62	.749
N1	66	64	.818
N2-3	27	49	.024
Pathological tumor size, cm			
0-2	64	69	.168
2.1-5.0	49	53	.887
≥ 5.1	25	37	.577
No. of positive nodes			
0	67	81	.271
1-3	70	56	.179
≥ 4	18	44	.005

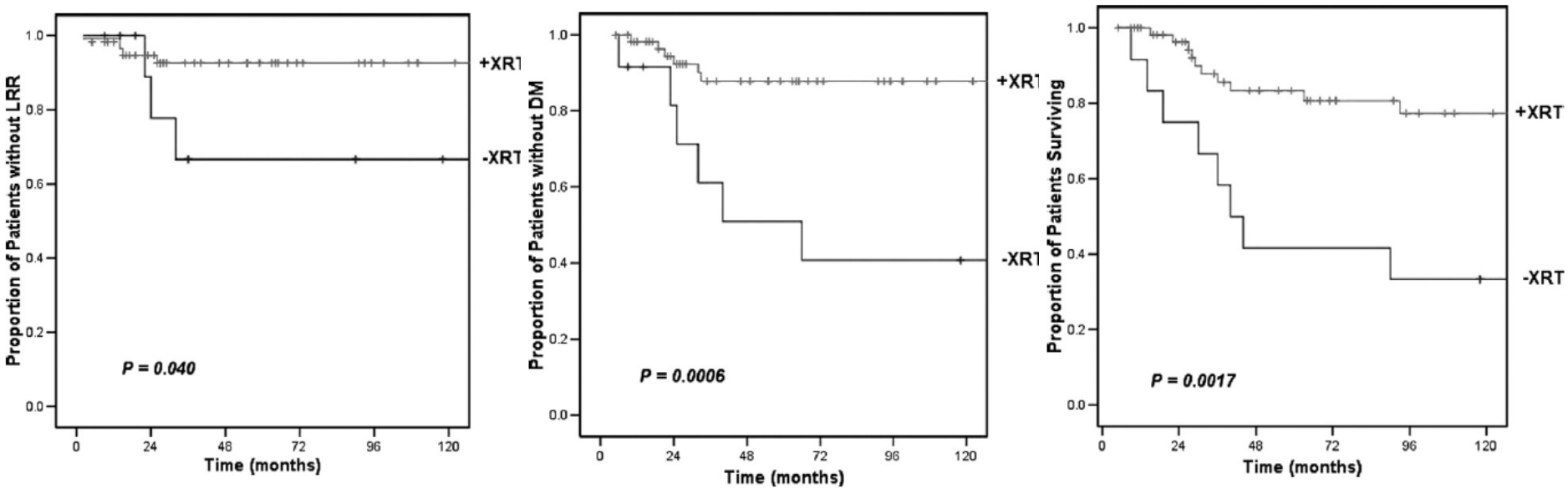
Abbreviation: CSS, cause-specific survival.

RT benefit ?

JCO 2004;22:4691-4699

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

- NAC+ mastectomy -> **ypCR**, 106 patients → PMRT (72 patients)
  → No PMRT (34 patients)
- ***Clinical stage III – PMRT benefit***



IJROBP 2007;68:1004-1009

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

- Clinical stage I or II, ypCR (32 patients) → **10 year LRR rate 0%**
- Clinical stage III, ypCR → **10 year LRR rate 7.3% (+RT) vs 33.3% (- RT)**

→ **Clinical stage III, pCR, mastectomy**

PMRT to chest wall, undissected draining nodal basin

IJROBP 2007;68:1004-1009

Retrospective studies from MDACC

- NAC, Mastectomy

→ ypCR (breast CR, LN (-))

→ **PMRT benefit for clinical stage III disease.**

- Limitation

① Retrospective analysis

② Her2/neu amplification : not routinely assayed

→ trastuzumab was not used!

Outcome of postmastectomy radiotherapy after primary systemic treatment in patients with clinical T1-2N1 breast cancer☆

- NAC+ mastectomy → **ypN0**, 53 patients
- China, France

- ypN0 → 5-year LRFS 94.7% (+ RT) vs. 72.9% (- RT)
  → 5-year DMFS 92.8% (+RT) vs. 75%(- RT)
  → 5-year DFS 92.9% (+RT) vs. 62.5% (-RT)

PMRT → LRFS, DMFS, DFS benefit

Retrospective analysis, unbalance sample size (83% patients PMRT)

Cancer Radiotherapie 2018;22:38-44

- The benefit of PMRT for patients with excellent response after neoadjuvant chemotherapy is still controversial

- No prospective randomized trial
- Different results between studies

RADIOTHERAPY FOR STAGE II AND STAGE III BREAST CANCER PATIENTS WITH NEGATIVE LYMPH NODES AFTER PREOPERATIVE CHEMOTHERAPY AND MASTECTOMY

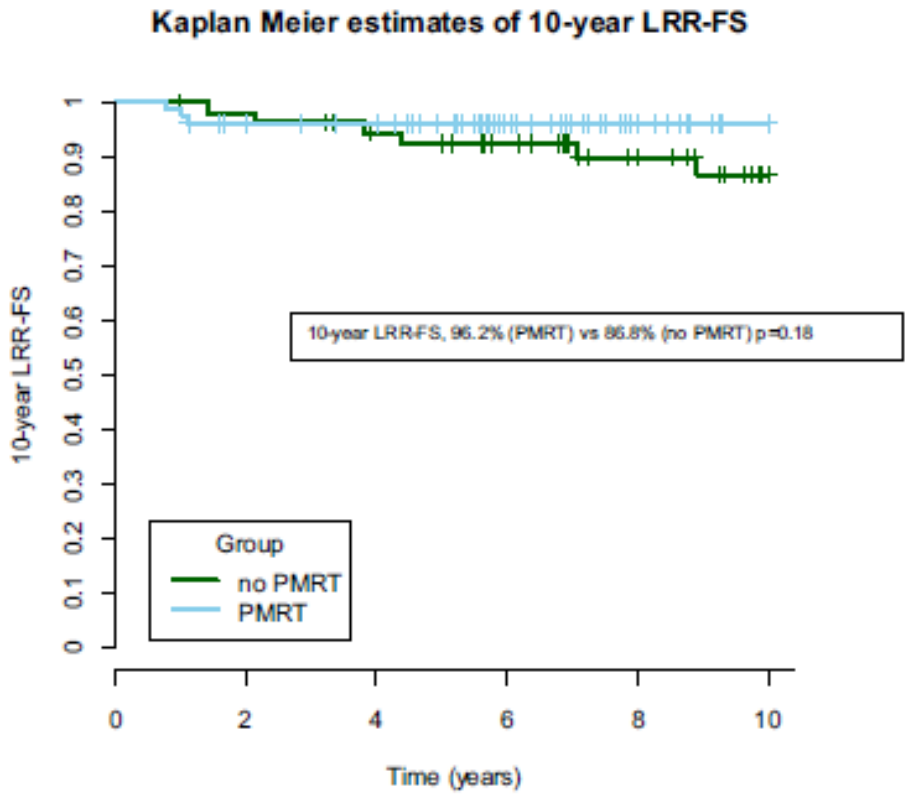
- NAC + mastectomy → **ypN0,** 134 patients
- France

Table 1. Patient characteristics and treatment

Variable	No PMRT group ($n = 56$)	PMRT group ($n = 78$)	p
Clinical Stage (AJCC)			.001
I	0	1 (1)	
II	44 (79)	39 (50)	
III	12 (21)	38 (49)	
Clinical T stage			.021
T1-T2	35 (62)	33 (42)	
T3-T4	21 (38)	45 (58)	
Clinical N stage			.007
N0	37 (66)	33 (42)	
N1-N2	19 (34)	45 (58)	
Primary tumor response to NAC (pCR)			.066
Yes	6 (11)	18 (23)	
No	50 (89)	60 (77)	

IJROBP 2012;82:e1-e7

RADIOTHERAPY FOR STAGE II AND STAGE III BREAST CANCER PATIENTS WITH NEGATIVE LYMPH NODES AFTER PREOPERATIVE CHEMOTHERAPY AND MASTECTOMY



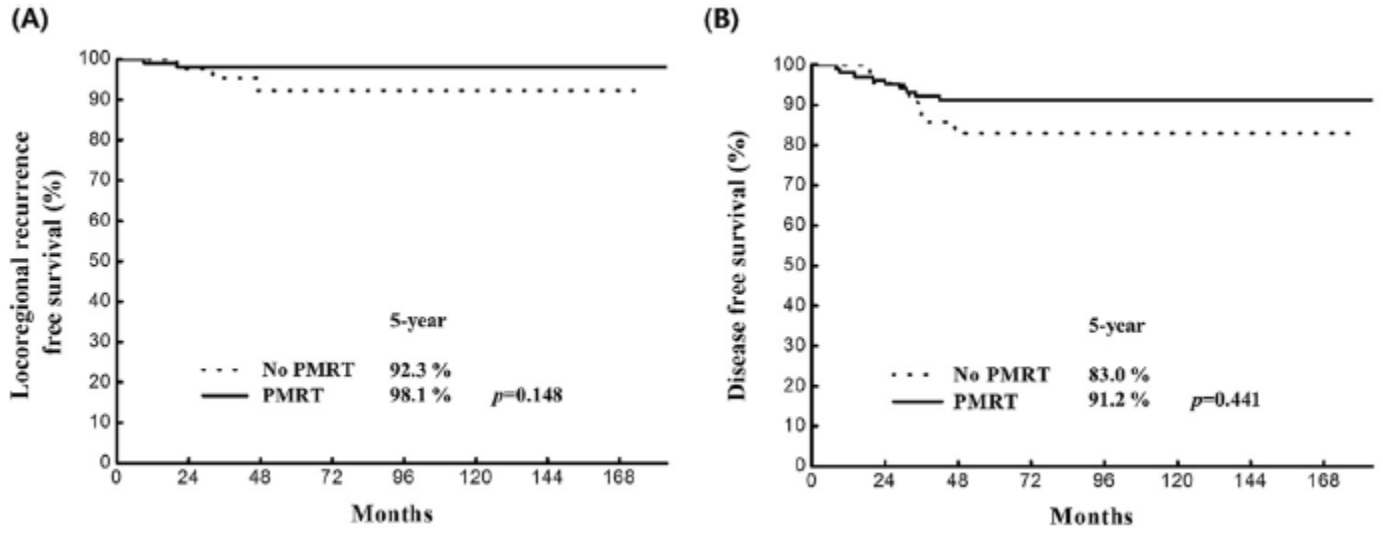
- **Multivariate analysis**

→ **PMRT no effect on LRR, DFS, OS**

IJROBP 2012;82:e1-e7

The Role of Postmastectomy Radiation Therapy After Neoadjuvant Chemotherapy in Clinical Stage II-III Breast Cancer Patients With pN0: A Multicenter, Retrospective Study (KROG 12-05)

- NAC + mastectomy → **ypN0,** 151 patients
- Korea



IJROBP 2014;88:65-72

The Role of Postmastectomy Radiation Therapy After Neoadjuvant Chemotherapy in Clinical Stage II-III Breast Cancer Patients With pN0: A Multicenter, Retrospective Study (KROG 12-05)

Table 5 Multivariate analysis of LRRFS, DFS, and OS (Cox model)

	LRRFS			DFS			OS		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age group ≤ 40 vs >40	0.149	0.230-0.959	.045	0.353	0.135-0.928	.035	0.935	0.246-3.550	.992
Clinical T Stage 1-2 vs 3-4	1.754	0.269-11.418	.557	1.059	0.371-3.019	.915	0.527	0.157-1.768	.299
Clinical N Stage N0 vs N1-N2				1.148	0.291-4.526	.844			
ypT stage 0-is vs 1 vs 2-4	2.294	0.594-8.858	.228	2.223	1.074-4.604	.031	1.775	0.770-4.092	.178
RT No PMRT vs PMRT	0.198	0.290-1.340	.097	0.647	0.236-1.772	.397	0.789	0.231-2.697	.705

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; LRRFS = locoregional recurrence-free survival; OS = overall survival; PMRT = postmastectomy radiation therapy; RT = radiation therapy.

- **PMRT; no effect on LRRFS, DFS, OS**

IJROBP 2014;88:65-72

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

- **Is PMRT indicated in patients with clinical stage I or II cancer who have NAST ?**

✓ **ypN(+) after NAC → PMRT**

✓ **ypN(-) after NAC → PMRT ?**

(*Although patients with no residual disease in either the breast or axillay nodes seem to have low rate of LRF, there are* ***insufficient data*** *to exclude the possibility that certain subgroups of these patients may still benefit from PMRT.*)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE SYSTEMIC THERAPY: ADJUVANT THERAPY

SURGICAL TREATMENT	ADJUVANT TREATMENT
	• Complete planned chemotherapy regimen course if not completed preoperatively. • Consider adjuvant capecitabine in patients with triple-negative breast cancer and residual

- Adjuvant radiation therapy[s] is based on maximal disease stage from prechemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results.
  - Post mastectomy:[s]
    - Strongly consider radiation to the chest wall + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk for clinical N1, ypN0.
    - For ANY positive axillary nodes after chemotherapy, radiation therapy as indicated to the chest wall + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk.

(category 1) ± pertuzumab. HER2-targeted therapy may be administered concurrently with radiation therapy and with endocrine therapy if indicated.[ff]

[m] See Surgical Axillary Staging (BINV-D).
[q] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[s] See Principles of Radiation Therapy (BINV-I).
[bb] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

[ff] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Radiation Oncology view for

- **Escalation**

→ Mastectomy : PMRT

→ **Breast conserving surgery : Breast + Regional lymph node RT**

→ Radiation dose escalation, radiosensitizer…..

- **De-escalation**

→ Mastectomy : omission of PMRT

→ **Breast conserving surgery : Breast RT only**

IS REGIONAL LYMPH NODE IRRADIATION NECESSARY IN STAGE II TO III BREAST CANCER PATIENTS WITH NEGATIVE PATHOLOGIC NODE STATUS AFTER NEOADJUVANT CHEMOTHERAPY?

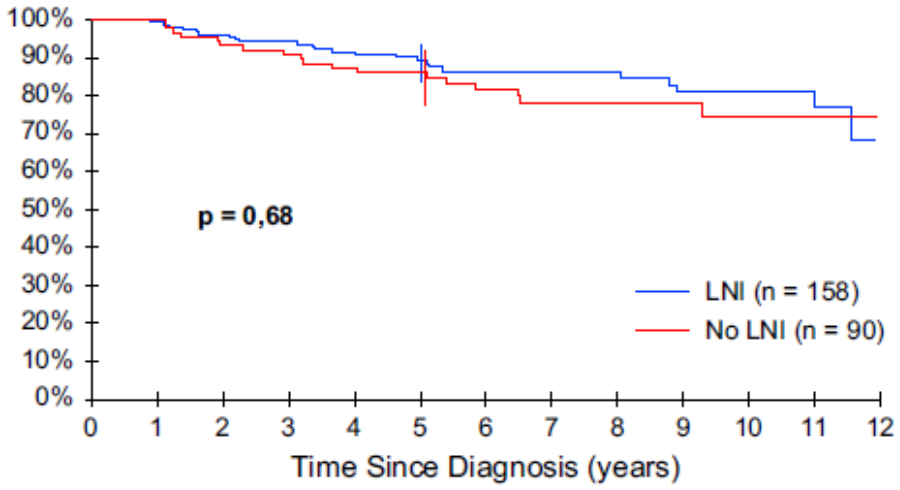
- NAC+ BCS → ypN0, 248 patients
- Breast irradiation; 50Gy
- **Breast irradiation + SCN+/- IMN irradiation 50Gy, 158 paients (63%)**

	LNI group N = 158		No LNI Group N = 90		
	No. of patients	%	No. of patients	%	*p*
Median age (range)	47 (20–71)		51 (28–72)		0.005
Age groups, years					
< 50	94	59.5	37	41.1	
50-59	39	24.7	35	38.9	0.04
60-69	23	14.6	17	18.9	
70+	2	1.2	1	1.1	
Clinical N					
N0	89	56.3	75	83.3	
N1	65	41.1	15	15.7	0.0001
N2	4	2.6	0	0	
Tumor localization					
Internal and/or central	102	64.6	15	16.7	<.00001
external	56	35.4	75	83.3	

IJROBP 2010;78:337-342

IS REGIONAL LYMPH NODE IRRADIATION NECESSARY IN STAGE II TO III BREAST CANCER PATIENTS WITH NEGATIVE PATHOLOGIC NODE STATUS AFTER NEOADJUVANT CHEMOTHERAPY?

5-yr LRR-FS, 89.4% (LNI) vs. 86.2% (no LNI), P = 0.68



5-yr OS, 88.7% (LNI) vs. 92% (no LNI), P = 0.32

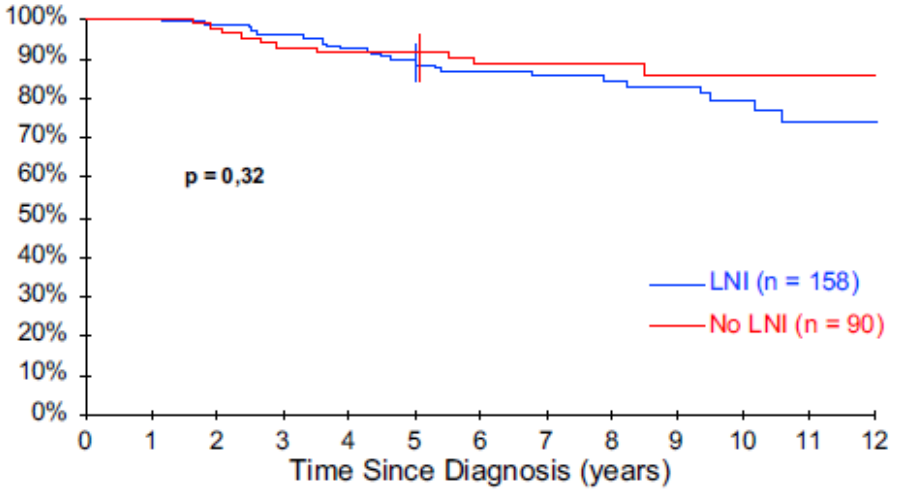


Table 2. Multivariate analysis of Overall survival, Cox Model (248 patients)

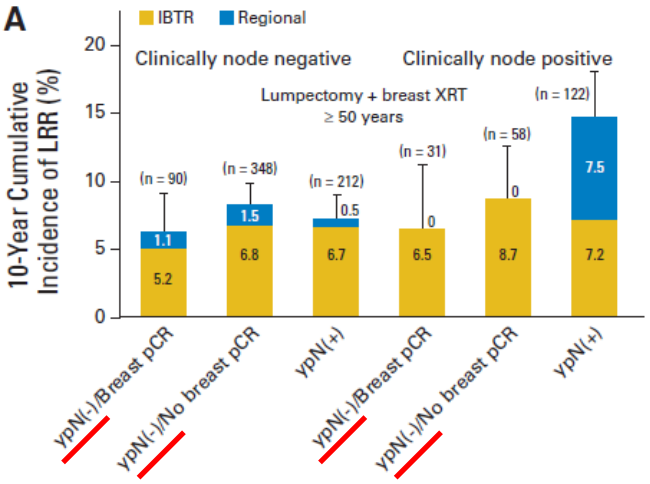
	HR for death	95% CI	*P*
Response to NAC			
pCR	1		
No pCR	3.05	1.17-7.99	0.023
Clinical Nodal status			
N0	1		
N1-N2	2.24	1.15-4.36	0.017

- **Regional nodal irradiation**
  → no effect on DFS, OS

IJROBP 2010;78:337-342

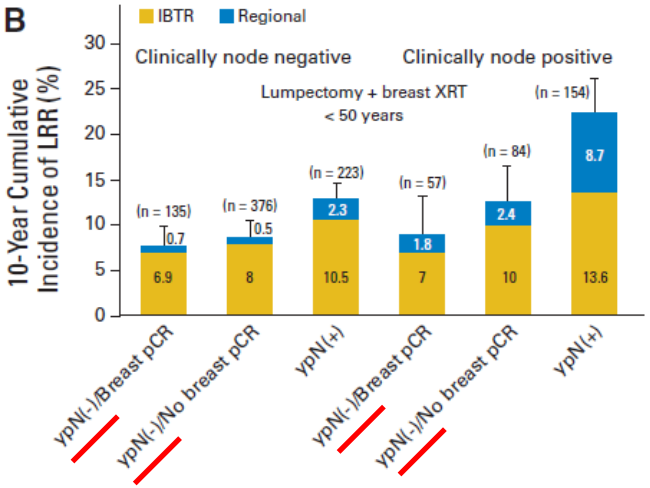
Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

- NAC → BCS+ **Breast RT (No RNI)**/ Mastectomy + **no RT**



≥ 50 years

- **ypN0**, regional nodal recurrence → 0 to 2.4%

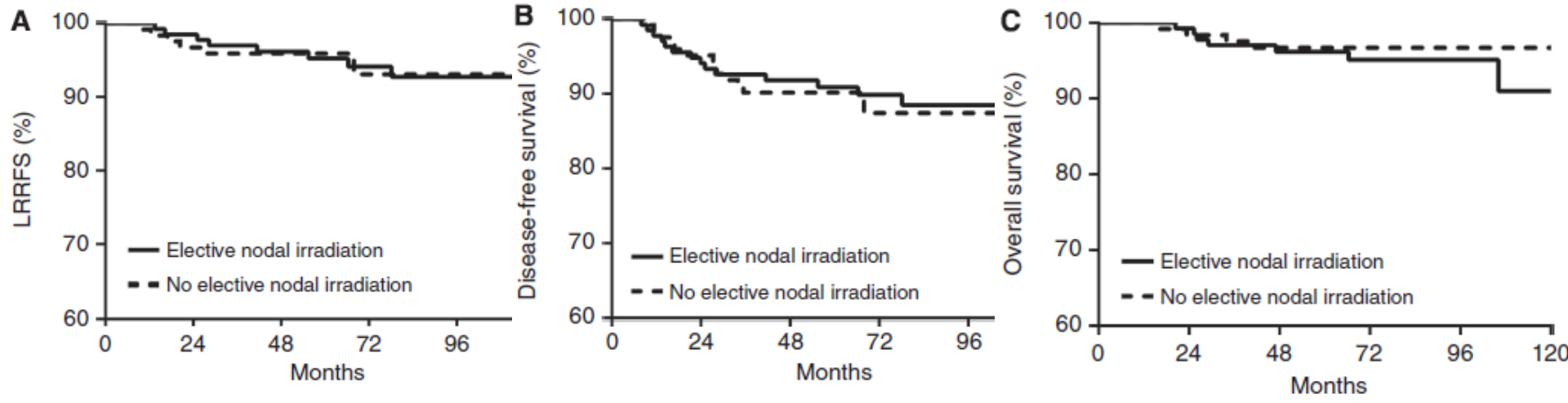


< 50 years

JCO 2012;30:3960-3966

Is elective nodal irradiation beneficial in patients with pathologically negative lymph nodes after neoadjuvant chemotherapy and breast-conserving surgery for clinical stage II–III breast cancer? A multicentre retrospective study (KROG 12-05)

- NAC + BCS → **ypN0**, 260 patients
- Breast RT 50.4Gy/28fx or 50Gy/25fx
- **Nodal irradiation in 136 patients (52%)**



BJC 2014;110:1420-1426

Is elective nodal irradiation beneficial in patients with pathologically negative lymph nodes after neoadjuvant chemotherapy and breast-conserving surgery for clinical stage II–III breast cancer? A multicentre retrospective study (KROG 12-05)

Table 4. Cox proportional hazards multivariate model for survival outcomes

	LRRFS		DFS		OS	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
ENI	1.187 (0.399–3.531)	0.7580	1.178 (0.543–2.560)	0.6782	1.670 (0.470–5.931)	0.4279
Age	–	–	0.542 (0.250–1.175)	0.1208	–	–
No. of sampled LNs	0.468 (0.161–1.363)	0.1638	0.374 (0.170–0.823)	0.0145	0.336 (0.097–1.164)	0.0853
Pathologic T classification	1.619 (0.764–3.429)	0.2085	2.025 (1.171–3.503)	0.0116	1.685 (0.710–4.001)	0.2369

Abbreviations: CI = confidence interval; DFS = disease-free survival; ENI = elective nodal irradiation; HR = hazard ratio; LN = lymph node; LRRFS = locoregional recurrence-free survival; OS = overall survival.

BJC 2014;110:1420-1426

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE SYSTEMIC THERAPY: ADJUVANT THERAPY

SURGICAL TREATMENT	ADJUVANT TREATMENT
	• Complete planned chemotherapy regimen course if not completed preoperatively. • Consider adjuvant capecitabine in patients with triple-negative breast cancer and residual invasive cancer following standard neoadjuvant treatment with taxane-, alkylator-, and anthracycline-based chemotherapy. and

- **Post lumpectomy:[s]**
  - Adjuvant radiation post-lumpectomy is indicated to the whole breast.
  - Strongly consider radiation to the whole breast + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk for clinical N1, ypN0.
  - For ANY positive axillary nodes after chemotherapy, radiation therapy as indicated to the whole breast + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk.

	and • If HER2-positive, complete up to one year of HER-2 targeted therapy with trastuzumab (category 1) ± pertuzumab. HER2-targeted therapy may be administered concurrently with radiation therapy and with endocrine therapy if indicated.[ff]

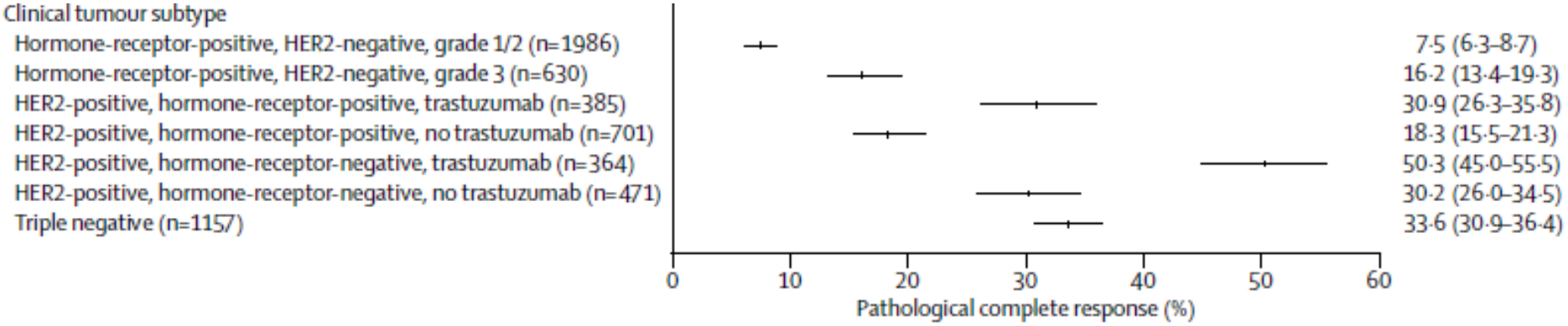
[m] See Surgical Axillary Staging (BINV-D).
[q] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[s] See Principles of Radiation Therapy (BINV-I).
[bb] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

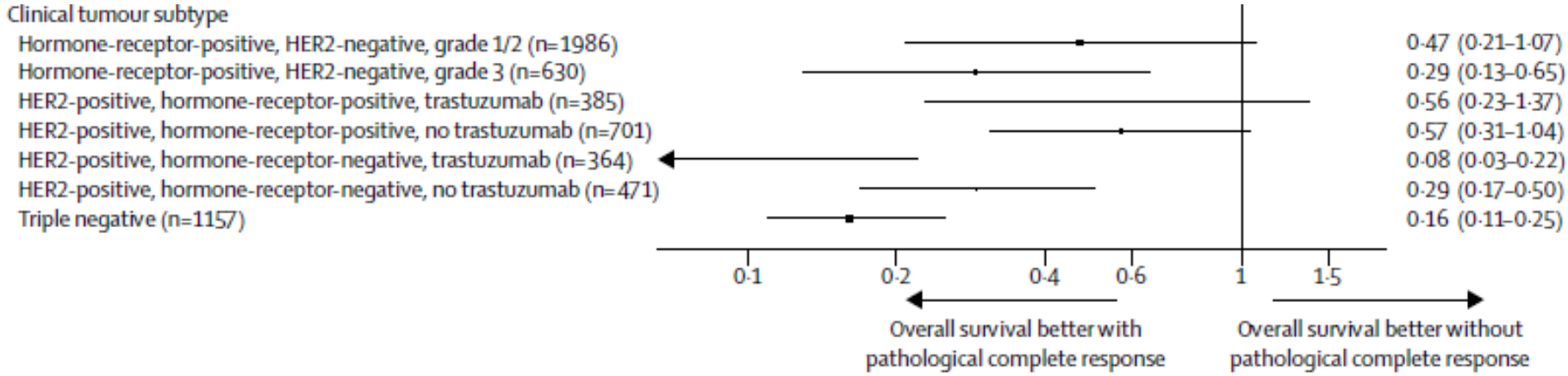
[ff] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Prognosis of pCR patient after neoadjuvant CTx in various breast cancer subtypes

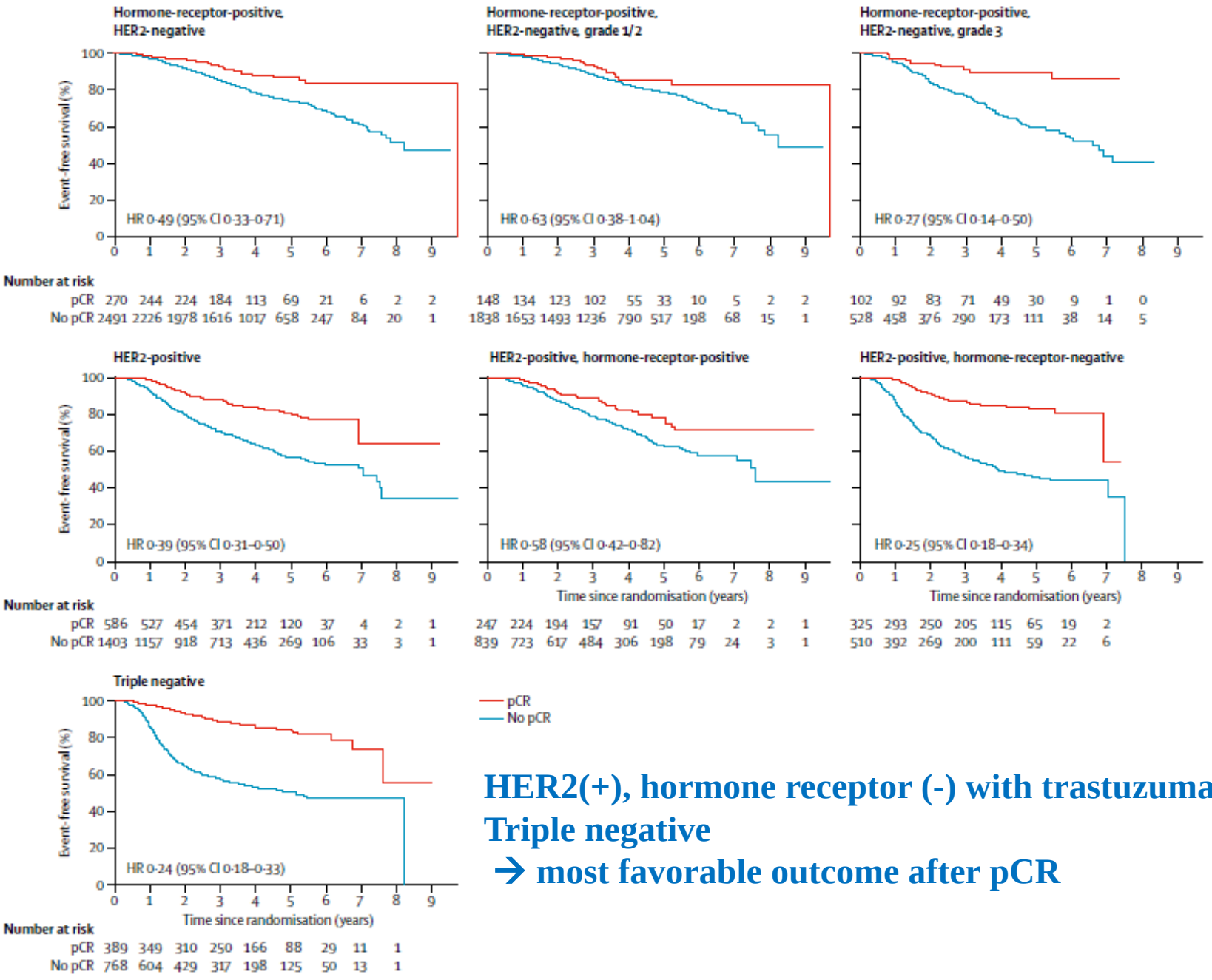
Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis





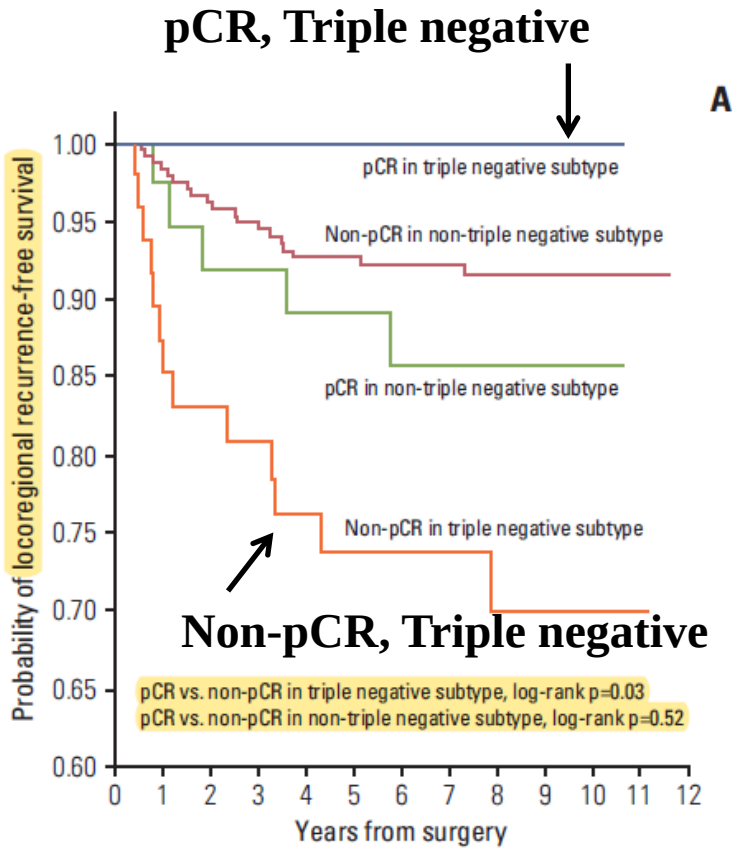
Triple negative, HER2 (+) with trastuzumab-> pCR ↑, survival ↑

Lancet 2014;384:164-172

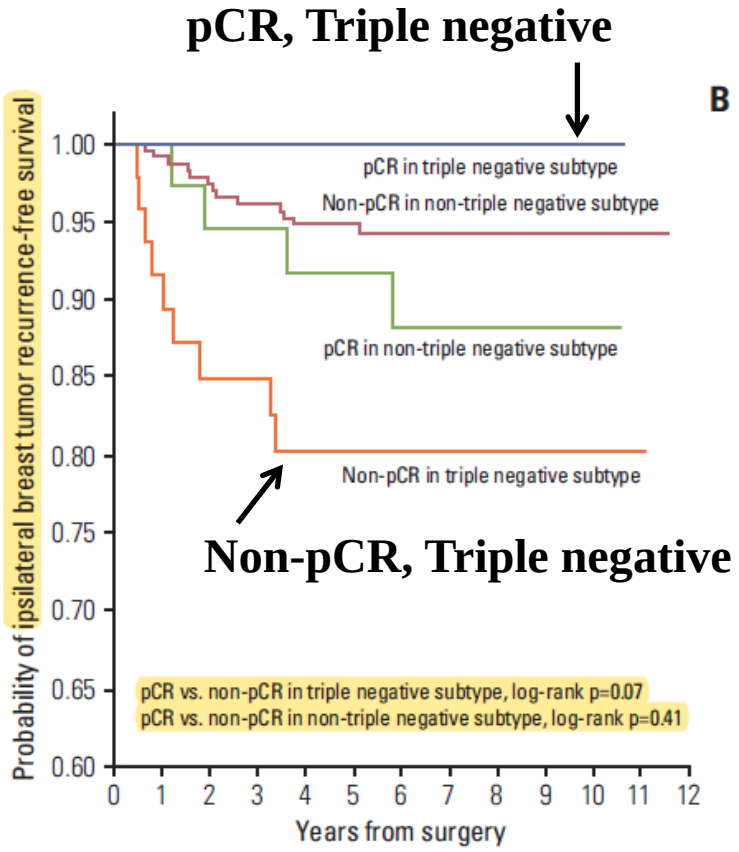


HER2(+), hormone receptor (-) with trastuzumab
Triple negative
→ most favorable outcome after pCR

Locoregional Recurrence by Tumor Biology in Breast Cancer Patients after Preoperative Chemotherapy and Breast Conservation Treatment



LRR



IBTR

Caner Res Treat 2016;48:1363-1372

Summary

- PMRT after mastectomy or regional nodal irradiation after breast conserving surgery for patients with excellent response after neoadjuvant systemic therapy might have no or small benefits.

- We cannot safely omit radiotherapy, because of lack of prospective randomized evidence.

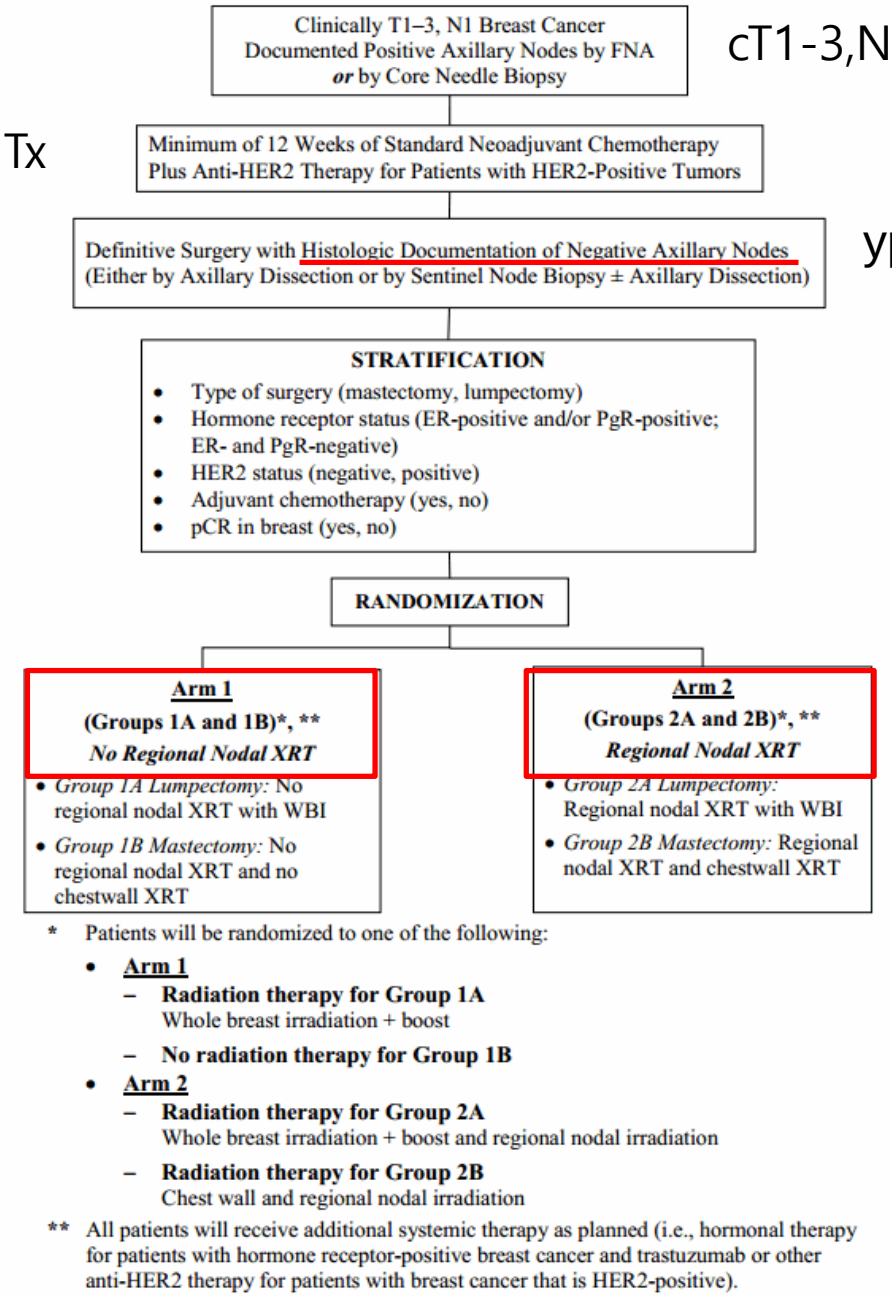
- Various tumor subtypes should be considered.

- Ongoing prospective trial (NSABP B51/RTOG1304)

NSABP B-51/RTOG 1304

neoCT, anti-HER2 Tx

Figure 1
NSABP B-51/RTOG 1304 Schema



* Patients will be randomized to one of the following:

- **Arm 1**
  - **Radiation therapy for Group 1A**
    Whole breast irradiation + boost
  - **No radiation therapy for Group 1B**
- **Arm 2**
  - **Radiation therapy for Group 2A**
    Whole breast irradiation + boost and regional nodal irradiation
  - **Radiation therapy for Group 2B**
    Chest wall and regional nodal irradiation

** All patients will receive additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and trastuzumab or other anti-HER2 therapy for patients with breast cancer that is HER2-positive).

Thank you for your attention!