Radiation Therapy after Neoadjuvant Chemotherapy in Breast Cancer

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NAC→ SX→ RT?

- Indication
  - NAC→ BCS→ all patients will receive WBI (RNI?)
  - NAC→ Mastectomy → PMRT?RNI?

RNI/PMRT after NAC?

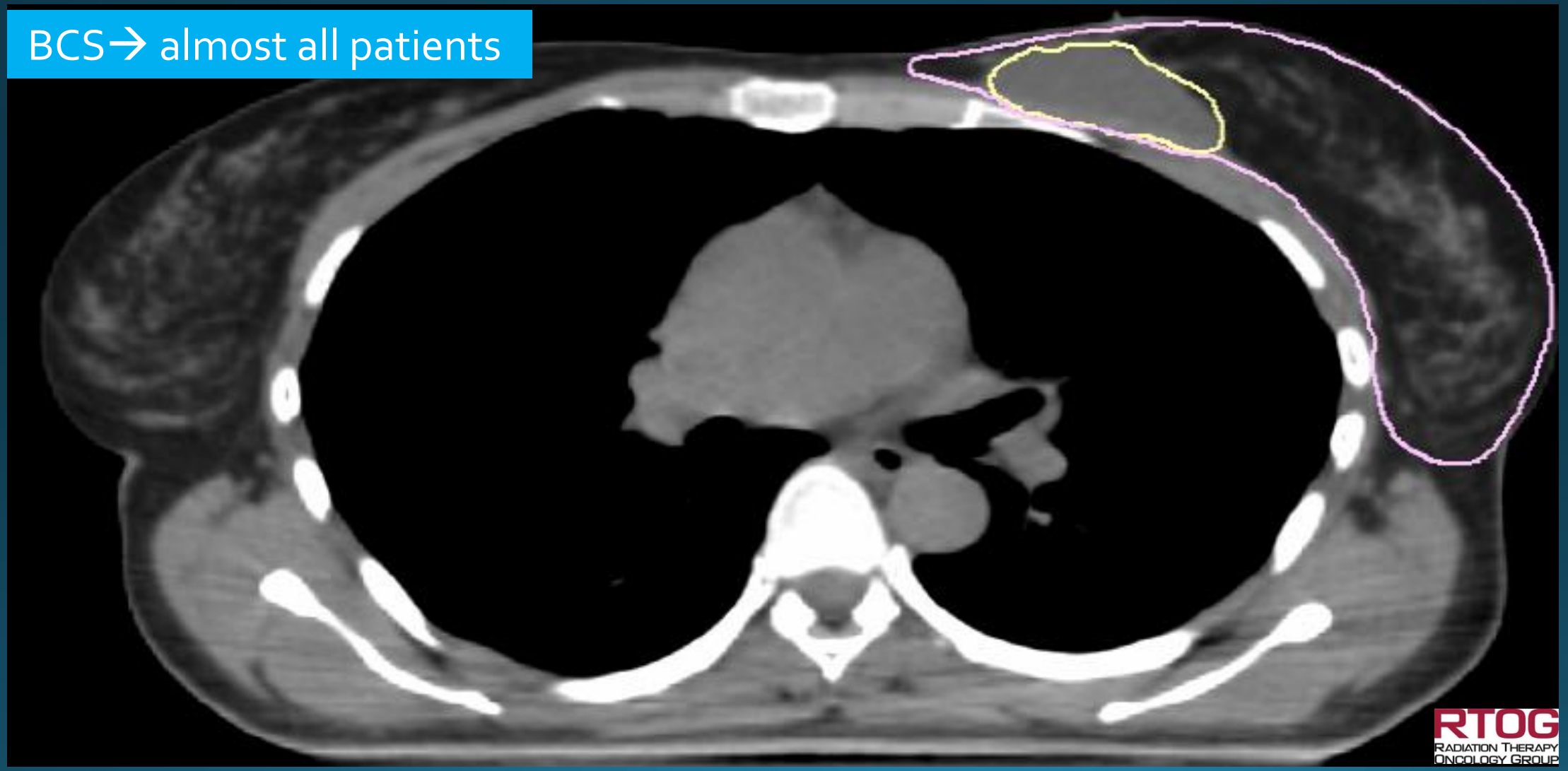
Tough cases for many Radiation Oncologists

BCS: Breast Conserving Surgery

WBI: Whole Breast Irradiation

PMRT: Post Mastectomy RT

Current indications of Adjuvant RT in BC



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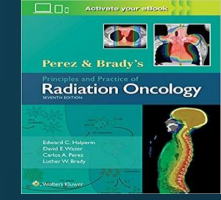


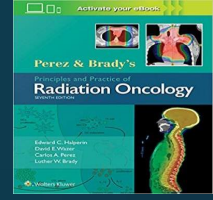
PMRT

- All T3 or T4, Node>=4
- node 1-3

EBCTCG, DANSH PMRT trial, British Columbia trial

RTOG
RADIATION THERAPY ONCOLOGY GROUP

Current indications of Adjuvant RT in BC



RNI → AMAROUS, MA20, EORTC22922

SC node

- Clinical N2 or N3 disease
- >4 +LN after axillary dissection
- 1–3 + LN with high-risk features

IMN

Individualized but consider for:

- Positive axillary nodes
- Central and medial lesions with high risk[a]
- Stage III breast cancer
- +SLN in the IM chain
- +SLN in axilla with drainage to IM on lymphosintigraphy

Axillary node

- N+ with extensive ECE
- SN+ with no dissection
- Inadequate axillary dissection
- High risk[a] with no dissection

RNI: Regional Nodal irradiation

RTOG Radiation Therapy Oncology Group

RT after NAC ?

- Our recommendation for ADJ RT is based on RCTs
- **Based on pathological information**

- NAC→ No upfront pathological information to assist decision making for PMRT and RNI

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How to make decision?

PMRT/RNI after NAC

- Studies
  - **Retrospective studies**
  - **Systematic reviews**
  - **RCT**

- Guidelines

How to make decision?

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

2012

- **NSABP B18 and B27**
  - **3088**
  - cT1-3No-1 breast cancer
  - NAC→ Sx (mastectomy/BCS) **without any RT**

- **Until the late 1990s**
- **(NSABP) did not allow PMRT or RNI after BCS**

provided us with the opportunity to examine:
- **rates and patterns of LRR in patients treated with NAC**
- **identify independent predictors ofLRRin this setting.**

Eleftherios P. Mamounas et. al.
JCO, DOI: 10.1200/JCO.2011.40.8369

NSABP B18 and B27

- The 10-year cumulative incidence of LRR

TABLE 61.2 SUMMARY OF RESULTS OF THE NSABP B18 AND B27 COMBINED ANALYSIS OF 10-YEAR LRR RISK AFTER NCT IN PATIENTS TREATED WITH MASTECTOMY

	ypN0; Breast pCR		ypN0; No Breast pCR		ypN+; Any Breast Response	
	N	10-year LRR	*N*	10-year LRR	*N*	10-year LRR
≤5 cm; cN0	46	6.5%	178	6.3%	184	11.2%
>5 cm; cN0	16	6.2%	95	11.8%	179	14.6%
≤5 cm; cN+	21	0%	37	10.8%	143	17.0%
>5 cm; cN+	11	0%	33	9.2%	128	22.5%

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Independent predictors of LRR in mastectomy patients:

- Clinical tumor size (before NAC)
- Clinical nodal status (before NAC)
- Pathologic nodal status/breast tumor response.

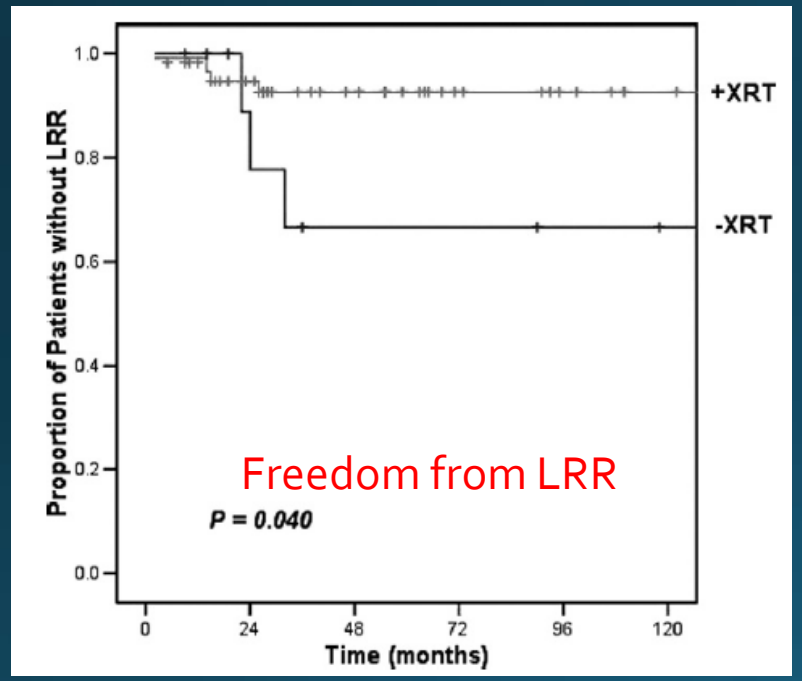
POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

- **MDACC retrospective study**
  - 226 patients in different stages
  - **PCR after NAC**
- Stage III
  - 10y LRR 33% → 7% with PMRT
- Stage I to II
  - low rates of LRR, irrespective of PMRT use

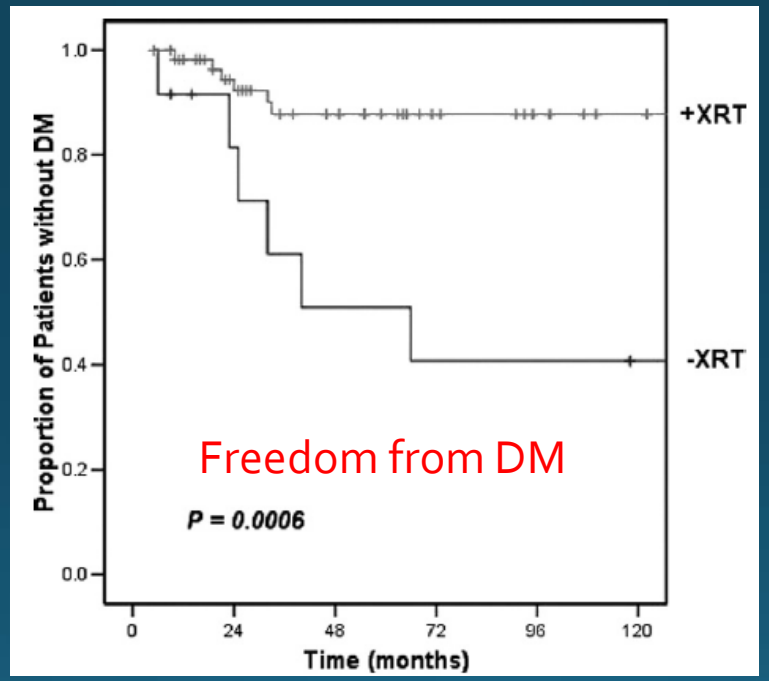
Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 4, pp. 1004–1009, 2007
S. E. MCGUIRE et al.

MDACC retrospective study

Stage III



Stage III



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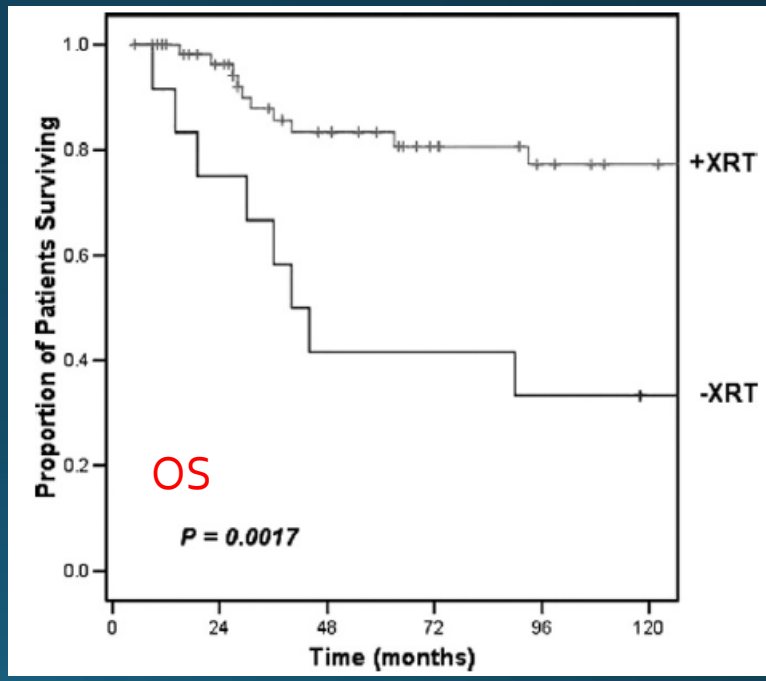

Conclusion:
Stage III disease despite having pCR to NACT have high LRR risk when PMRT was not used

Role of Postmastectomy Radiation After Neoadjuvant Chemotherapy in Stage II-III Breast Cancer

- A systematic review by Fowble et al.
- Included 24 studies
- 2011

- **To tailor recommendations for PMRT after NAC**

- **Women with a low risk of LRR for whom PMRT could be omitted?**

Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. 494e503, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.01.068

Role of Postmastectomy Radiation After Neoadjuvant Chemotherapy in Stage II-III Breast Cancer

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Conclusion:
- **Clinical stage II (T1-2No-1) patients**
- **Aged>40 years**
- **ER+**
- **PCR or 0-3 positive nodes without LVI or ENE**

→
- **<10 % risk of LRF without radiation**

Initial T3No tumors (stage IIB) who had a pCR were also considered low risk

cN1→NAC→ypNo→ PMRT/RNI?

FAQ

- MBC
  - Resection of primary and metastatectomy after good response to CHT?
  - Palliative Sx of breast?
- EBC
  - ADJ CHT or HT in Luminal A?
  - Sx plan? (BCS or Mas)
  - RT after NAC ? (CN1 → yPN0)
  - Eligibility for CHT? comorbidity or old age?
  - Approach to margin + ? (Referred by RO for Re excision)
- LRR
  - Re irradiation? ST?
- Pre Invasive
  - ADJ RT in DCIS?
- Rare cases
  - Phyllodes tumor
    - Further excision? ADJ RT? CHT?

cN1→NAC→ypNo→ PMRT/RNI?

The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis

→ PMRT :improved OS for all pathologic nodal subgroups (ypNo)

Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials

→ PMRT reduced LRR in cN+ → yPNo

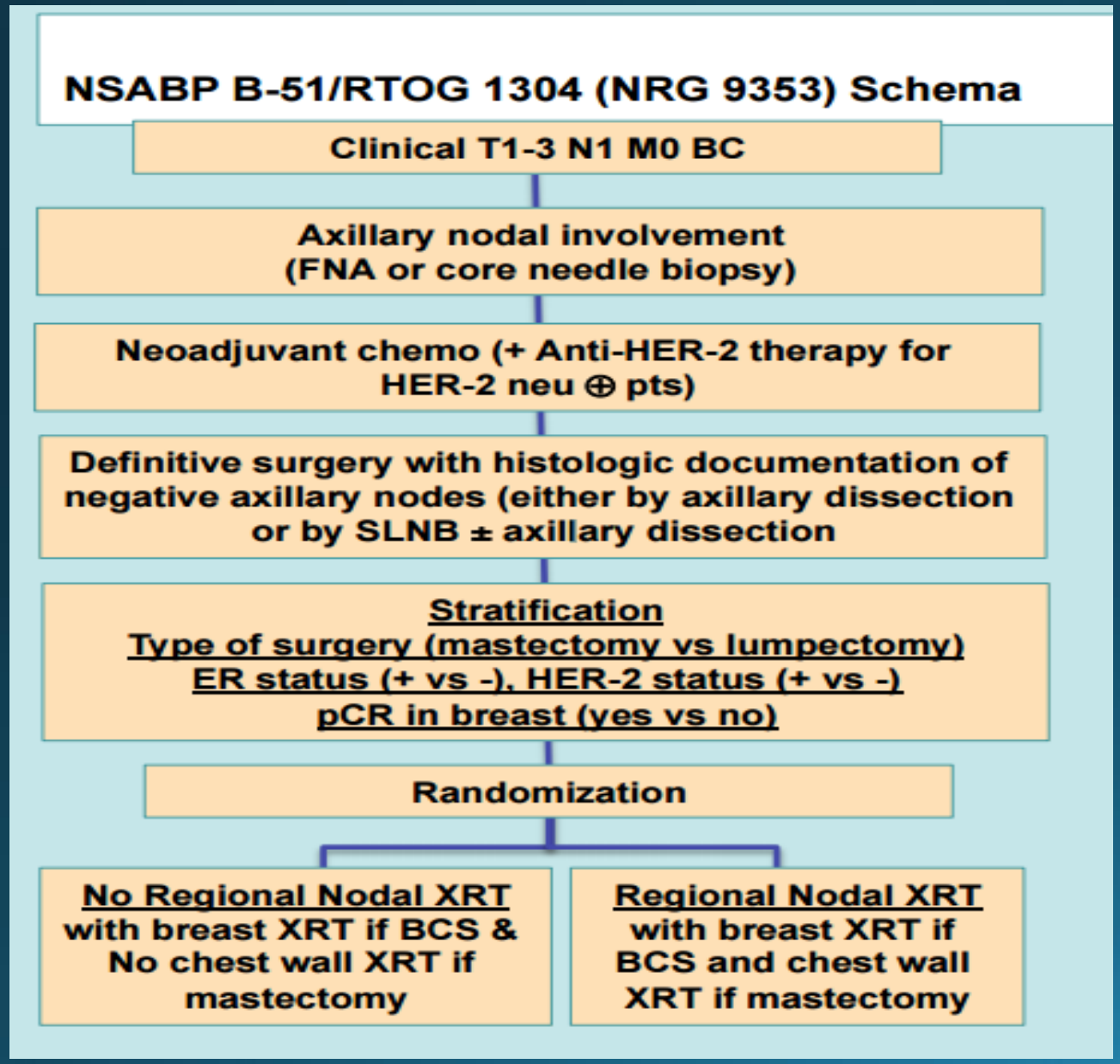
The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: a meta-analysis

→ PMRT might reduce local-regional recurrence for ypNo patients after NAC

Ongoing RCTs

- NSABP-B51/ RTOG 1304
- Alliance 011202

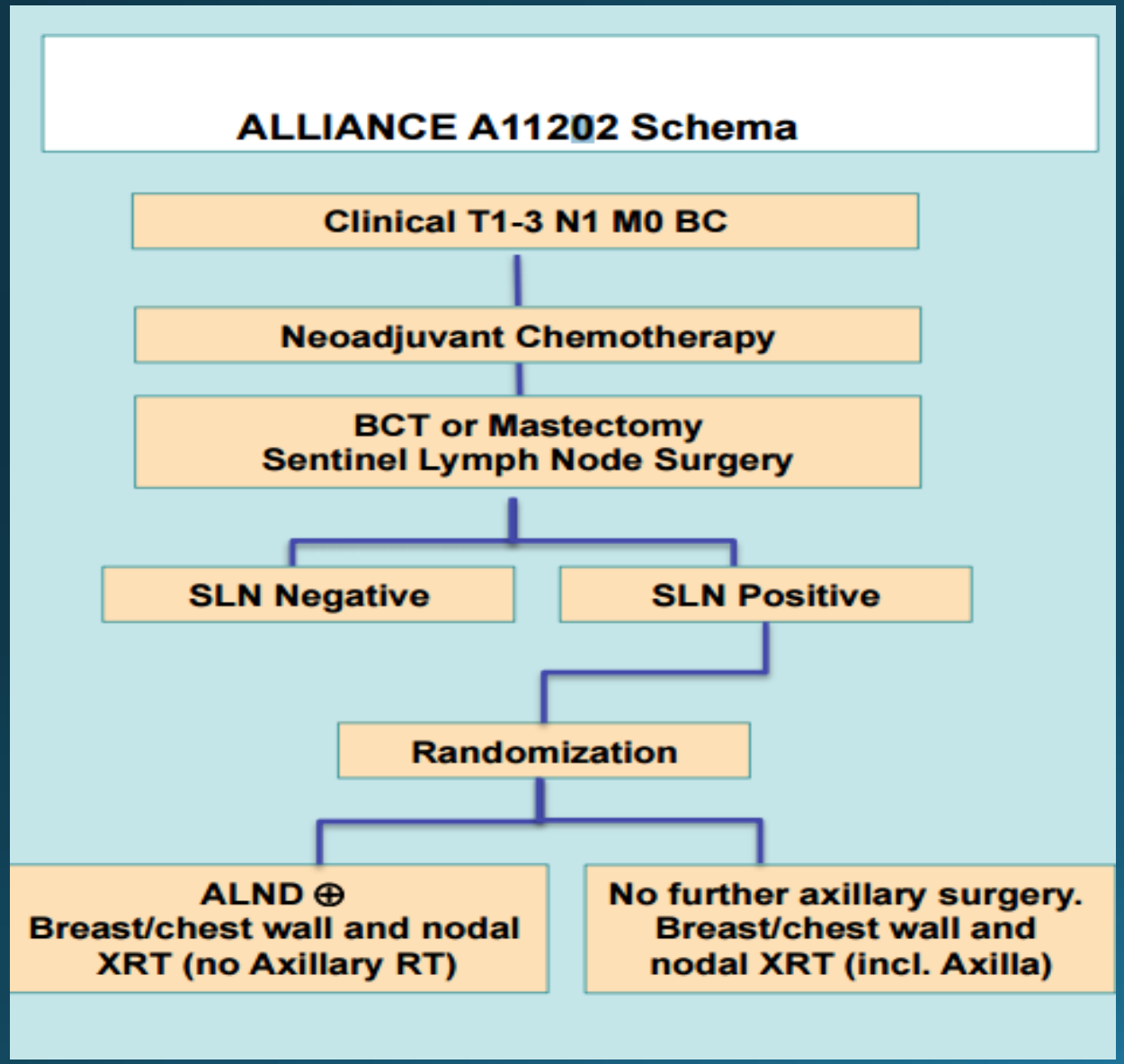
cN1→NAC→ypNo→ PMRT/RNI?



Phase III designed to answer whether RT improves breast cancer recurrence free interval in women who present with clinical N1 axillary disease before neoadjuvant chemotherapy and become No after (N2 and N3 disease not eligible)

Estimated Enrollment ℹ :	1636 participants
Study Start Date ℹ :	August 2013
Estimated Primary Completion Date ℹ :	July 2023
Estimated Study Completion Date ℹ :	August 2028

Accrual as of 2017 is 534 (32.64%)



Phase III trial designed to answer whether axillary node dissection improves rate of breast cancer recurrence over SLN alone when RT is delivered for clinically T1-3N1 tumors

NCCN 3.2014

Neoadjuvant Chemotherapy:
Indications for radiation therapy and fields of treatment should be based on the worst stage pretreatment or post-treatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

NCCN 1.2019

Radiation Therapy in Patients Receiving Preoperative Systemic Therapy

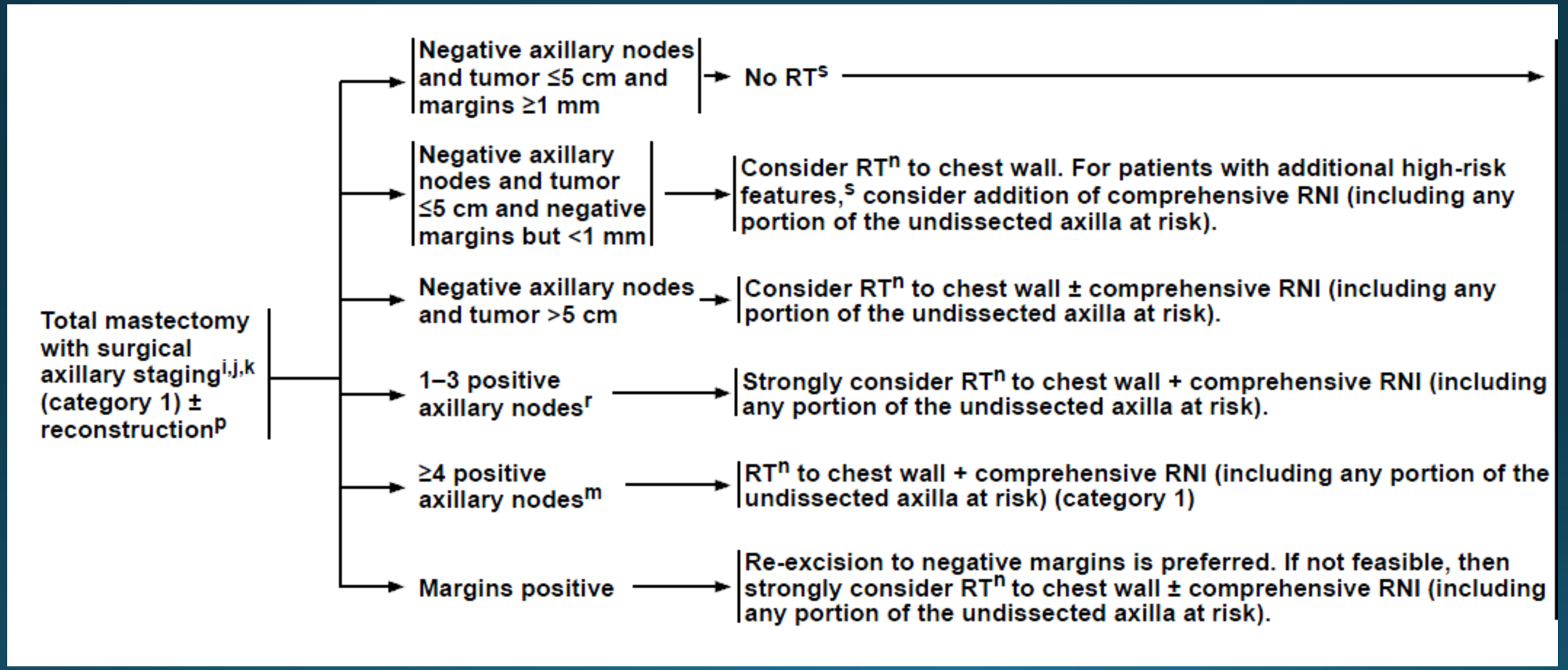
The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic chemotherapy should be made based on maximal stage from pre-chemotherapy tumor characteristics and/or pathological stage, irrespective of tumor response to preoperative systemic therapy.

NCCN 1.2022

- **Based on maximal disease stage (clinical, pathologic,…) at diagnosis (before preoperative ST) and pathology results after preoperative systemic therapy.**

Dose is similar for PMRT after adjuvant CHT or after NAC!

NCCN 1.2022
Sx→ CHT→ PMRT



NICE 2018, PMRT after NAC

- Offer:
  - Inflammatory breast cancer
  - yPN-positive (macrometastases) or involved resection margins. **yPN+**
  - Pretreatment investigations show node-positive (macrometastases) breast cancer **cN1**
- Consider :
  - Post-treatment histology shows node-negative T3 breast cancer
  - Pretreatment investigations show node-negative T3 breast cancer **cT3No**

Why the committee made the recommendations

There was not enough evidence to recommend subgroups of women in whom postmastectomy radiotherapy could be safely omitted after neoadjuvant chemotherapy. Therefore, the committee agreed that the recommendations for postmastectomy radiotherapy among people who have not received neoadjuvant chemotherapy applied to this population.

Summary
RT after NAC

- Stage III including those with PCR

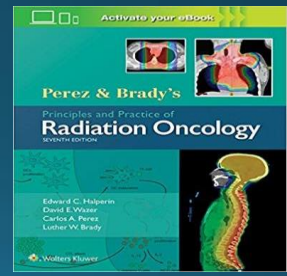
All cN2/N3/T4 and cT3N1 irrespective of response to NAC

- Pathologically positive nodes after NAC

yPN+

- Stage II patients
  - ASCO/ASTRO/SSO
    - Stage II→ ypNo
      - May have low rates of LRR → There remain insufficient data

- **cT1-2N1→yPNo**
- **cT3No**



Thank you…

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Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials

- Three NAC trials
- 817 non-inflammatory breast cancer patients
- 2019

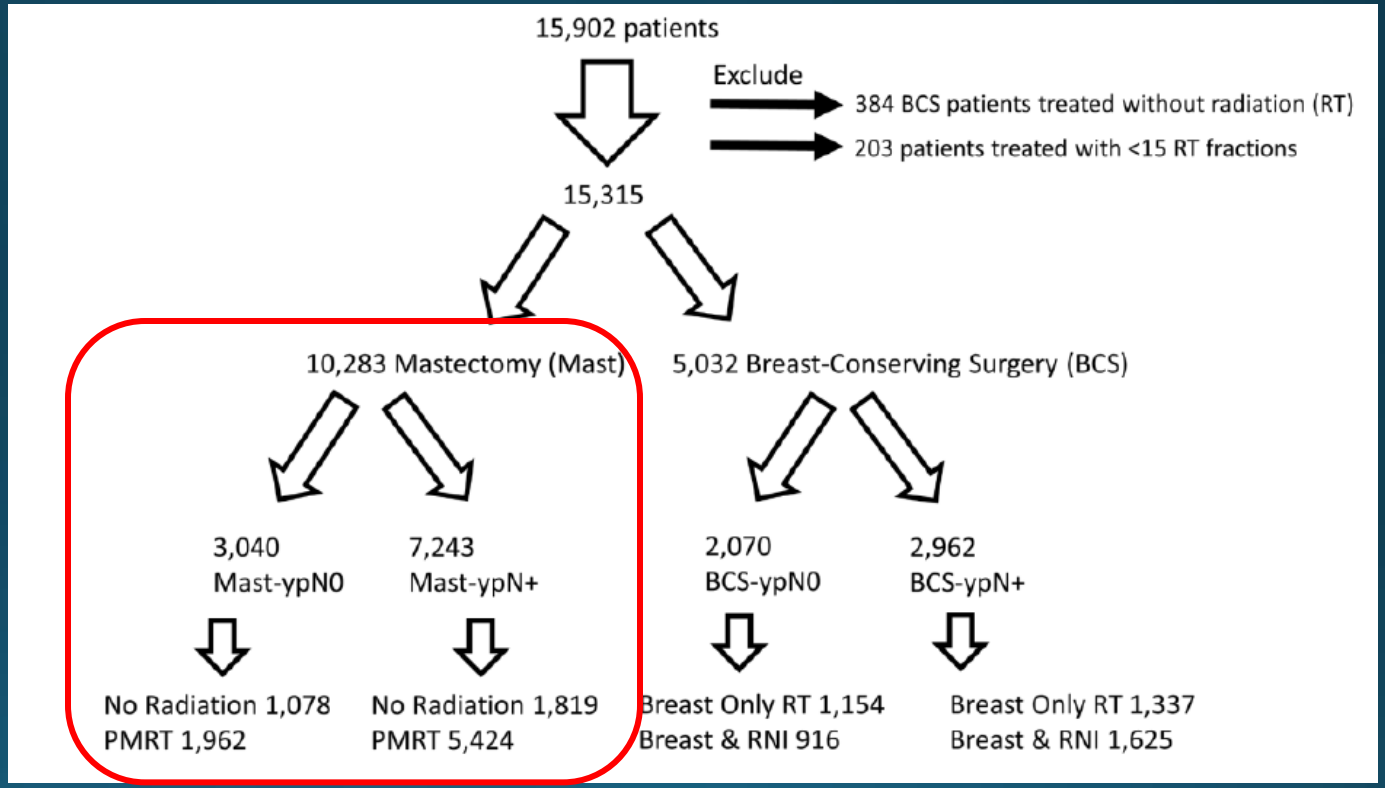
Results. The 5-year cumulative incidence of locoregional recurrence (LRR) was 15.2% (95% confidence interval [CI] 9.0–22.8%) in patients treated without RT and 11.3% in patients treated with RT (95% CI 8.7–14.3%). In the multivariate analysis, RT was associated with a lower risk of LRR (hazard ratio 0.51, 95% CI 0.27–1.0; $p = 0.05$). This effect was shown especially in patients with cT3/4 tumors, as well as in patients who were cN+ before neoadjuvant therapy, including those who converted to ypN0 after neoadjuvant therapy. In the bivariate analysis, disease-free survival was significantly worse in patients who received RT, however this was not confirmed in the multivariate analysis.

PMRT reduced LRR in cN+ → yPNo

Ann Surg Oncol (2019) 26:3892–3901
https://doi.org/10.1245/s10434-019-0763A5-x

PMRT in CN1 after NAC

- 2016 cT1-3-N1
- Rusthovenet al.



Conclusion:
PMRT was associated with improved OS for all pathologic nodal subgroups (ypNo, ypN1, ypN2-3)

The impact of postmastectomyand regional nodal radiation after neoadjuvantchemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysisC G Rusthovenet al.2Ann Oncol2016 May

The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: a meta-analysis 2021

Abstract

Background: It has been demonstrated that postmastectomy radiation therapy (PMRT) was beneficial for breast cancer patients who are axillary lymph node-positive. However, the effectiveness of radiotherapy in pathological negative nodes (ypN0) after neoadjuvant chemotherapy (NAC) remains open to considerable debate. Here, we aim to evaluate whether PMRT improves loco-regional control and survival for such patients.

Methods: The literature from January 2004 to June 2019 was searched. The effects of PMRT on local-regional recurrence (LRR) and survival was evaluated in a meta-analysis. Pooled relative risk (RR) values with 95% confidence intervals (CIs) were computed using random and fixed-effect model. Subgroup and heterogeneity analyses were also conducted.

Results: Twelve studies that included 17,747 patients met the inclusion criteria. Pooled results showed that PMRT was associated with reduced LRR (RR, 0.38; 95% CI, 0.19–0.77, $P = 0.007$), particularly in patients with stage III breast cancer (RR, 0.16; 95% CI, 0.07–0.37, $P < 0.001$). However, no significant difference in disease-free survival were observed with the addition of PMRT for ypN0 patients (RR, 0.70; 95% CI, 0.21–2.27, $P = 0.55$). Also, there was no statistically significant association between radiotherapy with overall survival (RR, 0.81; 95% CI, 0.64–1.04, $P = 0.10$).

Conclusions: Our meta-analysis indicated that PMRT might reduce local-regional recurrence for ypN0 patients after NAC, but lack of benefit for survival outcomes. Prospective randomized clinical trial data will be needed to confirm our results.

Wang et al. BMC Cancer (2021) 21:728
https://doi.org/10.1186/s12885-021-084231