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رادیوبیولوژی و پرستاری انکولوژی

29-31 January 2025
Olympic hotel,Tehran ,IRAN

RADIATION THERAPY IN THE SETTING OF pCR HAS TO BE BASED ON POST-TREATMENT ASSESSMENT

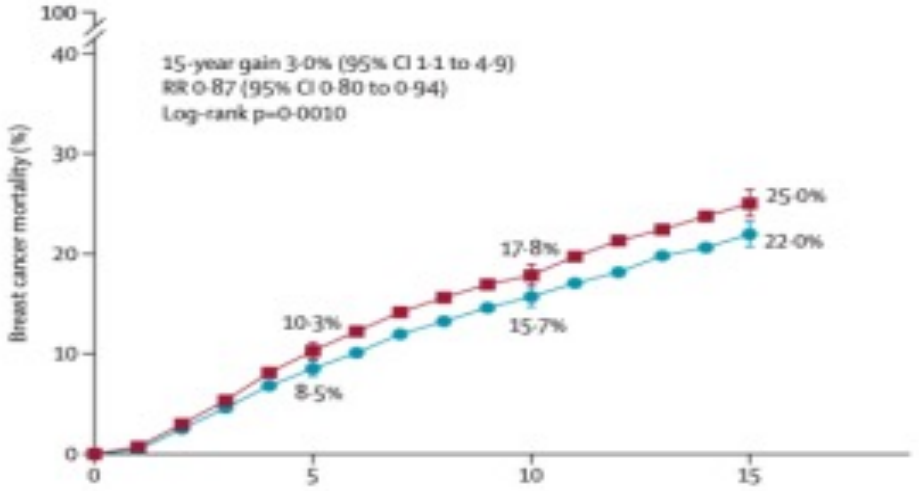
Controversy session

Dr. Elias Hassan Zadeh
Assistant Professor of Radiation Oncology
Hamadan University of Medical Sciences

History of Radiation roles in breast cancer: (primary surgery settings);

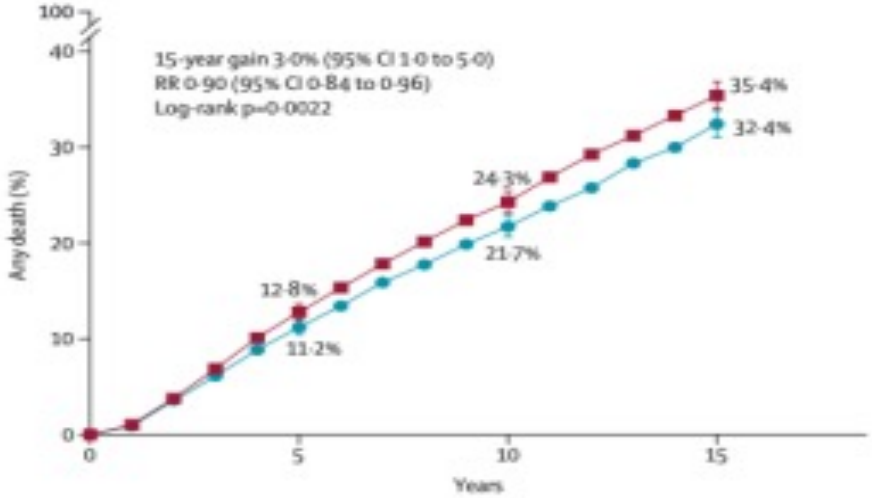
- **EBCTCG** showing reduction in **10-year risk of recurrence** in those who received WBRT versus those who did not (19% vs. 35%; RR, 0.52; 95% CI 0.48–0.56). In addition, **a significant reduction in 15-year risk of breast cancer death** (21% vs. 25%; RR, 0.82; 95% CI, 0.75–0.90) was also observed.
- The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the **MA.20 and EORTC 22922/10925** trials, and the reduction in breast cancer mortality with 15-year followup of **the EORTC 22922 patients, support the importance of RNI after BCS.**

EBCTCG:



Death rates (% per year: total rate minus rate in women without recurrence, 95% CI) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
1·76% (1·56–1·95)	1·66% (1·42–1·91)	1·55% (1·19–1·92)	1·11% (0·30–1·92)
2·14% (1·94–2·35)	1·80% (1·54–2·06)	1·87% (1·49–2·25)	0·98% (0·21–1·75)
0·82 (0·72–0·93)	0·92 (0·79–1·07)	0·83 (0·68–1·00)	1·22 (0·81–1·83)
−46·5/233·4	−13·8/170·3	−20·1/105·7	4·6/23·1



Any death rates (% per year [deaths per woman-years]) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
2·37% (660/27 902)	2·55% (554/21 743)	2·96% (382/12 916)	3·46% (128/3700)
2·70% (760/28 173)	2·83% (607/21 467)	3·14% (395/12 566)	2·99% (108/3606)
0·87 (0·78–0·97)	0·89 (0·79–1·00)	0·90 (0·78–1·04)	1·20 (0·91–1·58)
−47·0/334·5	−32·7/277·4	−18·6/183·9	9·3/50·8

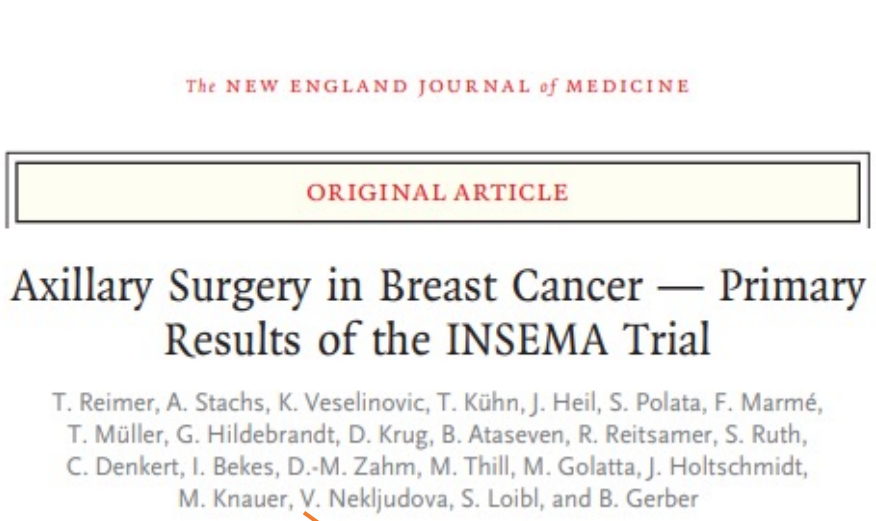
De escalations of axillary management in primary surgery:

- the AMAROS and OTOASOR trials showed that, in the setting of **primary surgery and a positive SLNB,** replacing ALND by Axillary RT (ART) yielded oncologically similar results, whilst reducing the risk of lymphoedema of the arm.

- The ACOSOG Z0011 trial and IBCSG 23–01 trials performed in the setting of **primary surgery and a positive SLNB**, even showed that omission of any further axillary treatment seems to be **oncologically safe,** in a group of patients of whom the far majority also underwent **whole breast RT and adjuvant systemic treatment.**

De escalations of axillary management in primary surgery:

More recent trials have gone a step further, by omitting SLNB in patients with cT1-2cN0 disease . INSEMA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

T. Reimer, A. Stachs, K. Veselinovic, T. Kühn, J. Heil, S. Polata, F. Marmé, T. Müller, G. Hildebrandt, D. Krug, B. Ataseven, R. Reitsamer, S. Ruth, C. Denkert, I. Bekes, D.-M. Zahm, M. Thill, M. Golatta, J. Holtschmidt, M. Knauer, V. Nekljudova, S. Loibl, and B. Gerber

DOI 10.1186/s12885-017-3443-x

BMC Cancer

STUDY PROTOCOL Open Access

Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial (BOOG 2013-08)

L. M. van Roozendaal[1,2†], M. L. G. Vane[1,2*†], T. van Dalen[3], J. A. van der Hage[4], L. J. A. Strobbe[5], L. J. Boersma[2,6], S. C. Linn[7], M. B. I. Lobbes[8], P. M. P. Poortmans[9], V. C. G. Tjan-Heijnen[2,10], K. K. B. T. Van de Vijver[11], J. de Vries[12], A. H. Westenberg[13], A. G. H. Kessels[14], J. H. W. de Wilt[15] and M. L. Smidt[1,2]

omission of surgical axillary staging was noninferior to sentinel-lymph-node biopsy
after a median follow-up of 6 years. (

In summary, in the setting of primary surgery, regional treatment is increasingly being individualized:

1**) no SLNB and no axillary treatment at all in low risk patients**, to

2) **omitting ALND or replacing ALND by ART in cN0/pN+ (SLNB) patients**, and to

3) **ALND in combination with RT of Level 3 & 4 nodes with or without inclusion of IMN, especially in patients with pN2 disease**

Radiation in the setting of pCR has to be adapted to post-treatment assessment

Primary systemic therapy(neaoadjuvant):

PST however has important :

1)the response can be monitored, which can be motivating for the patient to continue systemic treatment, and it can be used to adapt systemic treatment;

2) the patient is allowed more time to think about the surgical options, for which sometimes genetic analysis may be required;

3) downstaging of the tumour yields a higher chance of safe breast conserving surgery

4) downstaging of axillary nodes may allow de-escalation of the nodal treatment

axillary pCR can be reached in patients with initially involved nodes in 44 up to even 97% in ER negative Her2 positive tumours ,there is an increasing demand for de-escalation of axillary treatment.

Heterogeneity in Outcomes among Women with Clinically Node-positive Breast Cancer and Axillary Pathologic Complete Response: An Analysis of *NSABP B18, B27, B40, and B41*

- B18 and B27 did not include HER2-directed therapy,
- B40 enrolled women with HER2- disease,
- B41 enrolled those with HER2+ disease.
- B40 and B41 allowed RNI at the physicians' discretion.
- We evaluated LRR, DR ,DFS, and OS among 4 strata of pCR: ypT0/ypN0; ypT+/ypN0; ypT0/ypN+; ypT+/ypN+

Median follow-up for B18, B27, B40, and B41 was 13.7, 9.7, 4.5, and 5.1 years, respectively, and included 742, 2254, 1154, and 504 women for analysis.

cN+ women with apCR in B18 and B27 (combined) with bpCR had better OS than those without bpCR (p Z 0.02) with 5-year OS rates (95% CI) of 90% (85%, 96%) vs 80% (75%, 86%).

For **B40 and B41, RNI was discretionary but administered more commonly to those with larger tumors (median [IQR]: 5.0 [3] vs 4.0 [3] cm, p<0.01) and those without bpCR (68% vs 58%, p<0.01) or apCR (54% vs 26%, p<0.01).**

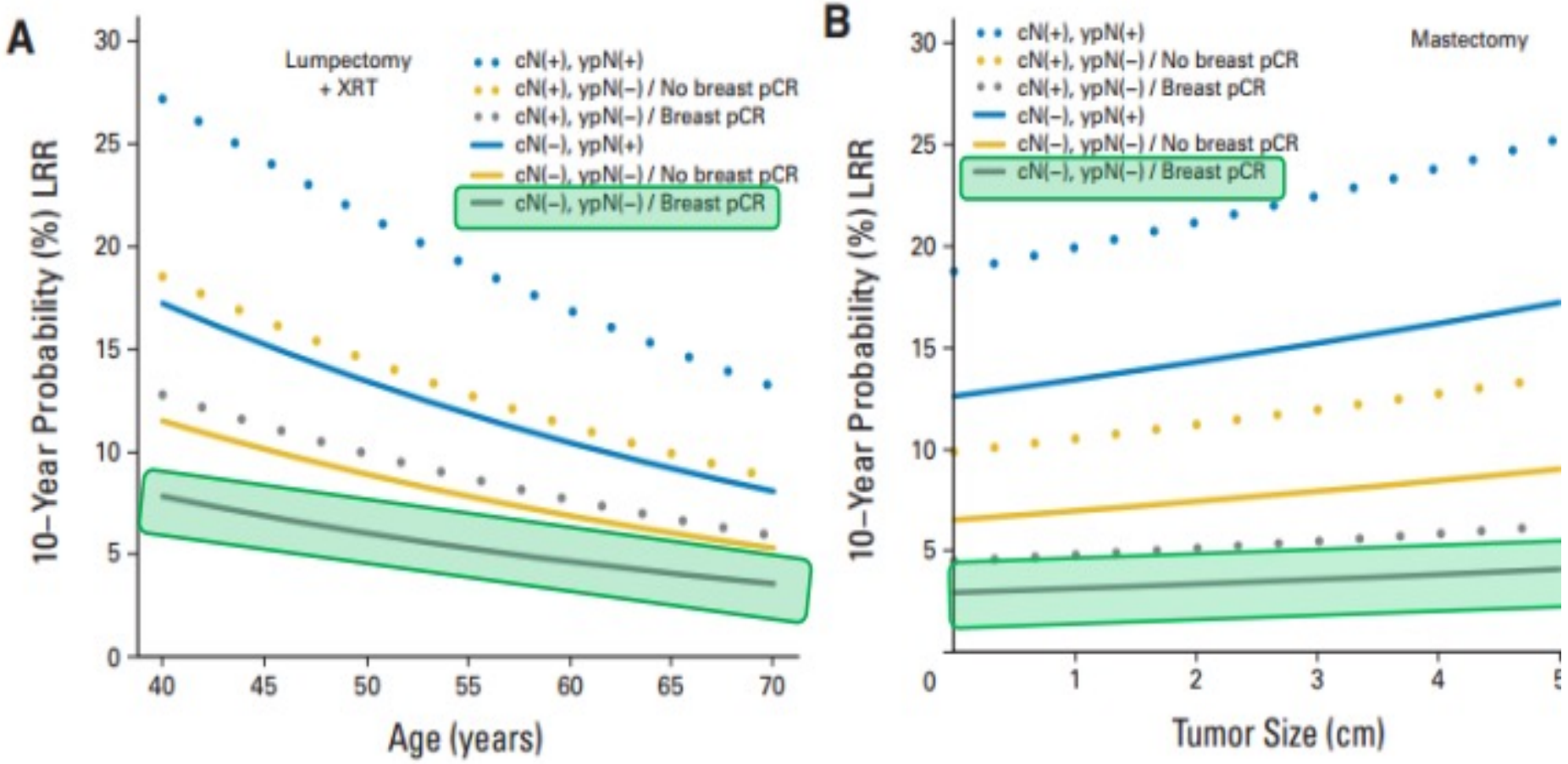
cN+ women in B40 and B41 (combined) with apCR with bpCR had better OS than those without bpCR (p Z 0.008) with 5-year OS rates (95% CI) of 96% (93% - 99%) vs 86% (80% - 93%), and reduced CIF of DR (p Z 0.02) with 5-year CIF rates (95% CI) of 8% (5% - 12%) vs 14% (9% - 21%)

De-escalation of regional nodal radiotherapy after PST and ALND

- 2012, Mamounas performed a combined analysis of the **NSABP B-18 and B-27 trials,** in which patients were treated with **PST followed by breast conserving surgery or mastectomy including ALND**. RT was limited to the breast in case of breast conserving surgery; **no RNI was given**.
- This analysis showed that **ypT and ypN-status were independent predictors for LRR both after breast conserving therapy and mastectomy**

RT following PST & pCR: *Current knowledge*

Combined analysis of NSABP B18 and B27



Breast Cancer Res Treat
DOI 10.1007/s10549-017-4359-5

BRIEF REPORT

From clinical trials to clinical practice: outcome of NSABP-B27 neoadjuvant chemotherapy regimen for high-risk early-stage breast cancer

Hikmat Abdel-Razeq[1] · Lina Marei[1] · Salwa S. Saadeh[1] · Hazem Abdulelah[1] · Mahmoud Abu-Nasser[1] · Mourad Salam[1] · Walid Daana[1] · Basel Al-Haj Ali[1] · Ayat Taqash[2]

Received: 16 June 2017 / Accepted: 23 June 2017

Clinical Trial > Lancet Oncol. 2015 Sep;16(9):1037-1048. doi: 10.1016/S1470-2045(15)00041-8. Epub 2015 Aug 10.

Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial

Harry D Bear [1], Gong Tang [2], Priya Rastogi [3], Charles E Geyer Jr [4], Qing Liu [2], André Robidoux [5], Luis Baez-Diaz [6], Adam M Brufsky [7], Rita S Mehta [8], Louis Fehrenbacher [9], James A Young [10], Francis M Senecal [11], Rakesh Gaur [12], Richard G Margolese [13], Paul T Adams [14], Howard M Gross [15], Joseph P Costantino [2], Soonmyung Paik [16], Sandra M Swain [17], Eleftherios P Mamounas [18], Norman Wolmark [19]

Affiliations + expand

PMID: 26272770 PMCID: PMC4624323 DOI: 10.1016/S1470-2045(15)00041-8

JOURNAL ARTICLE

Preoperative Chemotherapy in Patients With Operable Breast Cancer: Nine-Year Results From National Surgical Adjuvant Breast and Bowel Project B-18

Norman Wolmark, Jiping Wang, Eleftherios Mamounas, John Bryant, Bernard Fisher

JNCI Monographs, Volume 2001, Issue 30, December 2001, Pages 96–102,
https://doi.org/10.1093/oxfordjournals.jncimonographs.a003469
Published: 01 December 2001

> Clin Cancer Res. 2020 Aug 15;26(16):4233-4241. doi: 10.1158/1078-0432.CCR-20-0152. Epub 2020 May 5.

NSABP B-41, a Randomized Neoadjuvant Trial: Genes and Signatures Associated with Pathologic Complete Response

Sandra M Swain [1 2], Gong Tang [2 3], Heather Ann Brauer [4], David S Goerlitz [5], Peter C Lucas [2 3], André Robidoux [2 6], Brent T Harris [5], Hanna Bandos [2 3], Yuqi Ren [4], Charles E Geyer Jr [2 7], Priya Rastogi [2 3 8], Eleftherios P Mamounas [2 9], Norman Wolmark [2 3]

Affiliations + expand

PMID: 32371537 PMCID: PMC7724952 DOI: 10.1158/1078-0432.CCR-20-0152

- surgery and ALND, and RNI was left to the discretion of the physician. In univariate analysis, only patients with ypN + Her2+ disease who received RNI had improved overall survival when compared to non-irradiated patients; **whereas improved LRR was seen in B-40 pa tients with ypN + hormone receptor positive disease**

Conclusion: of *NSABP B18, B27, B40, and B41*

In women with cN+ypN0 on B-18 and B-27 for which no HER2-directed therapy was offered, **residual breast disease was associated with worse OS than bpCR**.

While in the modern NCTX trials cN+ women with higher risk disease received RNI with HER2-directed therapy, ypN0 women with residual breast disease continue to demonstrate worse survival and DR than women with bpCR, despite apCR.

However, in the multivariable analysis of the B-40 and B-41 study populations, **RNI was not found to be significantly associated with improved OS, disease-free survival, distant recurrence, or LRR.**

In the absence of level I data, we advise caution in omitting RNI off trial in women with cN+ ypN0 disease with residual breast disease

Clinical Trial > JAMA. 2013 Oct 9;310(14):1455-61. doi: 10.1001/jama.2013.278932.

Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node–positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial

Judy C Boughey [1], Vera J Suman, Elizabeth A Mittendorf, Gretchen M Ahrendt, Lee G Wilke, Bret Taback, A Marilyn Leitch, Henry M Kuerer, Monet Bowling, Teresa S Flippo-Morton, David R Byrd, David W Ollila, Thomas B Julian, Sarah A McLaughlin, Linda McCall, W Fraser Symmans, Huong T Le-Petross, Bruce G Haffty, Thomas A Buchholz, Heidi Nelson, Kelly K Hunt; Alliance for Clinical Trials in Oncology

Affiliations + expand

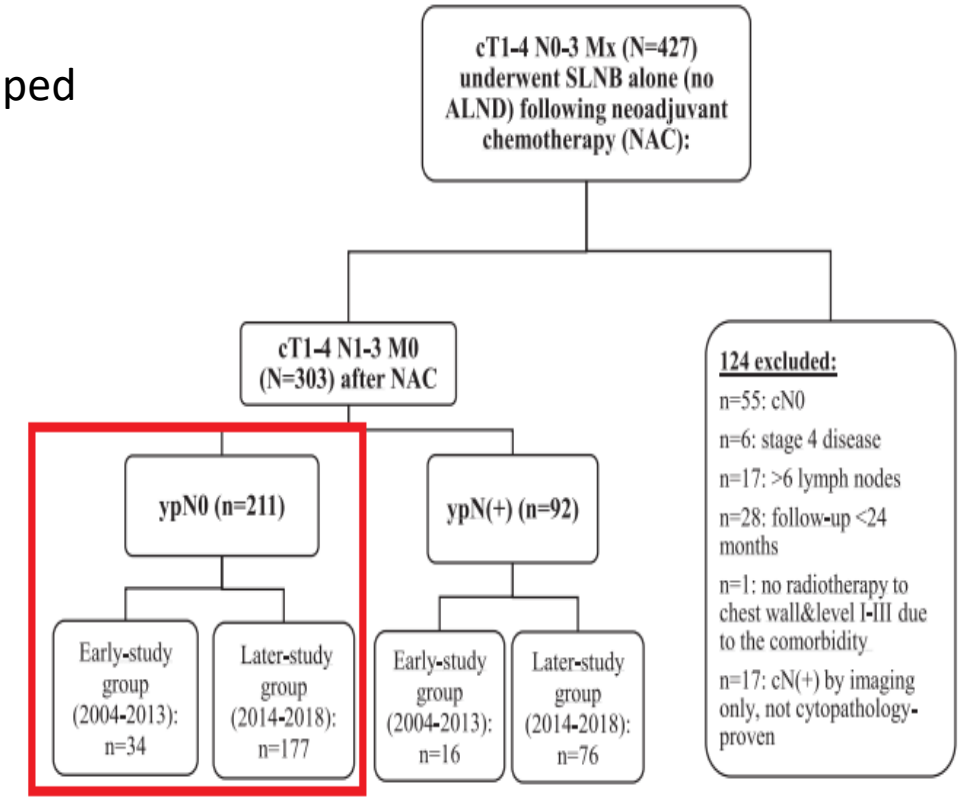
PMID: 24101169 PMCID: PMC4075763 DOI: 10.1001/jama.2013.278932

ACOSOG 1071 trial (Alliance), which included patients with **stage I-III disease**. They found that **locoregional RT did lower the 5-yr LRR rate in patients with ypN + disease, but not in patients with ypN0 disease**

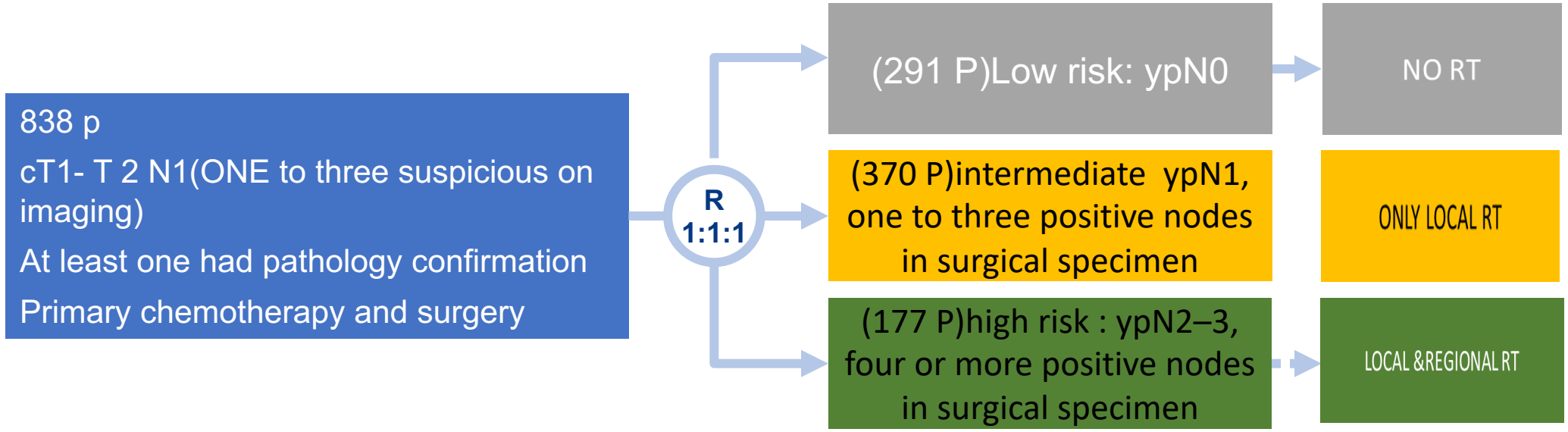
NEOSENTI-TURK MF-18-02

211 patients with cN+, ypN0 (SLNB) were treated with RNI (axilla level 1–4) instead of ALND. **Only one patient** developed **a nodal recurrence 60 months** after treatment

No difference in 5-year DFS between patients with ypN0 (SLNB) disease and ypN1mi (SLNB), in whom ALND was omitted as well



The *RAPCHEM* registry is the first study providing prospective data on de-escalation of postoperative RT according to response to PST in cT1–2 N1 breast cancer patients.



CO-PRIMARY ENDPOINTS

- **LRR**

BIOMARKER ENDPOINTS

- Other risk factors were used to assign patients who did not receive ALND, and were identified as follow: **tumour grade 3, lymph vascular invasion, and tumour size ≥3 cm.**

RAPCHEM trial :

Radiotherapy consisted of a biologically equivalent dose **of 25 fractions of 2** Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was **forward-planned or inverse-planned intensity modulated radiotherapy**

	LOW RISK	INTERMEDIATE RISK	HIGH RISK
5 YEARS LRR	2.1%	2.2 %	2.3%

RAPCHEM trial;

Interpretation:

In this study, **the 5-year locoregional recurrence rate was less than 4%,** which **supports our hypothesis that it is oncologically safe to de-escalate locoregional** radiotherapy based on locoregional recurrence risk, **in selected patients with cT1–2N1 breast cancer treated with primary chemotherapy**, according to this predefined, consensus-based study guideline.

triple negative disease was an independent predictor for LRR, even in the ypN0 groups.

The aim of this meta-analysis was to gather the current evidence and investigate the impact of adjuvant LRRT on breast cancer patients with clinical T3 and/or lymph node metastatic disease and pCR after NACT.

Contents lists available at ScienceDirect

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journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Review Article

Adjuvant locoregional radiation therapy in breast cancer patients with pathologic complete response after neoadjuvant chemotherapy: A systematic review and meta-analysis

Normehr Nikyar [a], Eva Tegnelius [b], Antonis Valachis [b,*]

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[b] Department of Oncology, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden

The concept of adjuvant radiotherapy in the present study included both the local radiation therapy to the chest wall after mastectomy and the LRRT to breast or chest wall and to regional lymph nodes after mastectomy or breast conserving surgery

13 studies were included in the meta-analysis

Table 1
Study characteristics of the 13 eligible studies.

Author (year) [Ref]	Country	Type of study	Multicentric	Enrollment years	Number of patients	Age at diagnosis and molecular subtype in study cohorts	Median follow-up (months)	ITB adjustment	Covariates in multivariate analyses
Cho (2019) [21]	Korea	Retrospective	Yes	2005–2011	189	>50 yrs old 43.4%; Luminal 45.5%, HER2-positive 25.9%, TNBC 28.6%	78.0	No	Grade, LVI, endocrine therapy
Fayanju (2020) [27]	USA	Retrospective with prospectively collected data	Yes	2004–2015	6183	Median age 51 (IQR: 43–60); Luminal 40%, HER2-positive 34.4%, TNBC 24.1%	40.1	No	Age, radiation, race/ethnicity, insurance status, grade, cT stage, Charlson/Deyo comorbidity score, facility type, facility location, extent of axillary surgery, histology, tumor subtype
Haffty (2019) [26]	USA	Retrospective with prospectively collected data	Yes	2009–2011	248	Luminal 59.6%, HER2-positive 32.8%, TNBC 26.3%	70.8	Yes	cT stage, in- breast pCR, tumor biology
Huang (2020) [20]	China	Retrospective	Yes	2000–2014	282	Median age 49 (range; 20–79); Luminal 50.1%, HER2-positive 30.9%, TNBC 19.0%	72.9	No	Age, cT stage, cN stage, LVI, molecular subtype, ypT, endocrine therapy, adjuvant chemotherapy
Kantor (2017) [28]	USA	Retrospective with prospectively collected data	Yes	2004–2008	1937	<50 yrs old 46.1%, 50–70 yrs old 46.6%, >70 yrs old 7.3%	69	No	Age, race, insurance, charlson comorbidity index, histology, grade, ER-status, PR-status, endocrine therapy, cT stage, ypT stage
Le Scodan (2012) [23]	France	Retrospective	No	1990–2004	134	Mean age 49.9 (range: 28–71)	91.4	No	Age, cT stage, cN stage, histologic stage, inflammatory signs, endocrine therapy, NACT regimens, ER-status, PR-status response to NACT
Liu (2016) [16]	USA	Retrospective	No	1998–2009	1046	Median age 50 (range: 20–88)	56.0	Yes	Age, race, insurance status, histologic grade, cT stage, ypT stage, no. of examined regional nodes, clinical stage, endocrine therapy
Miyashita (2019) [24]	Japan	Retrospective with prospectively collected data	Yes	2004–2009	1297	Median age 53 (range: 23–92)	NR	No	Age, cT stage, cN stage, biological subtype
Rusthoven (2016) [25]	USA	Retrospective with prospectively collected data	Yes	2003–2011	3040	Age < 50 yrs old 55.8%, >50 yrs old 44.2%	39	Yes	Age, race, year of diagnosis, Charlson/Deyo comorbidity score, grade, cT stage, in-breast pCR, ypN, extent of axillary surgery, ER-status, endocrine therapy
Shim (2014) [22]	Korea	Retrospective	Yes	1998–2009	151	Median age 47 (range: 27–78); Luminal 41.1%, HER2-positive 13.9%, TNBC 24.5%	59	No	Age, cT stage, cN stage, ypT
Wang (2020) [13]	China	Retrospective	No	2004–2016	48	Median age 50 (range: 23–64); Luminal 54.2%, HER2-positive 19.8%, TNBC 19.8%	72	No	Age, clinical stage
Zhang (2020) [14]	Taiwan	Retrospective with prospectively collected data	No	2007–2015	1423	Median age 51 (IQR: 44–59)	NR	Yes	Age, diagnosis year, Charlson comorbidity index, tumor differentiation, clinical stage, ypT, ypN, NACT regimen, nodal surgery, ER-status, PR-status, HER2-status, hospital type

Impact of LRRT on LRR, DFS, and OS in patients with axillary pCR

LRR

. In total, 2388 patients with N+ at diagnosis and ypN0 after NACT were included in the analysis, 859 received LRRT and 1529 did not

results showed a statistically significant reduced risk of LRR in patients who received LRRT (HR 0.59; 95% CI 0.42–0.81; P = 0.001)

DFS

A total of 2019 patients were included in the analysis out of which 626 received LRRT and 1393 did not

no statistically significant difference between the LRRT and no LRRT groups (HR 1.00; 95% CI 0.75–1.33; P = 0.99

OS

, nine studies were eligible including 14,991 patients out of which 8281 were treated with LRRT and 6710 without LRRT

NOsignificant difference between the LRRT and no LRRT groups (HR 0.92; 95% CI 0.82–1.03; P =

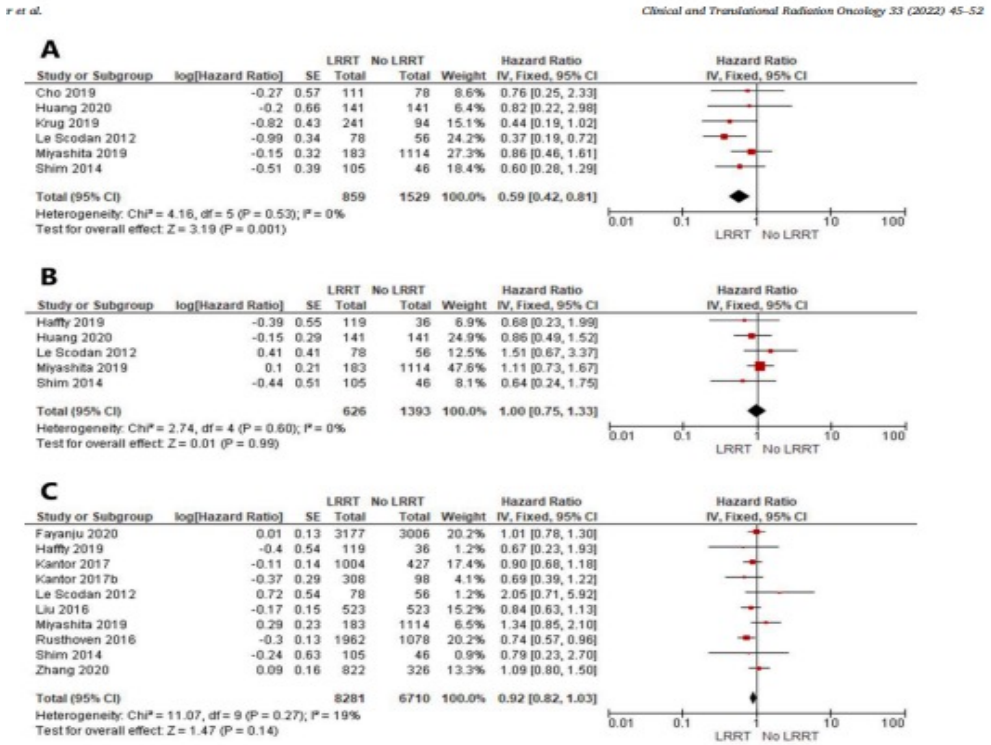
the results should be interpreted in clinical practice with caution considering the low certainty of evidence. Results from the ongoing randomized trial are anticipating to provide results with high level of evidence for this complex clinical situation.

Table 3

Certainty of the evidence on pooled analyses according to GRADE-approach.

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
Locoregional recurrence	HR 0.59 (0.42 to 0.81)	2388 (6 observational studies)	⨁⨁ LOW
Disease-free survival	HR 1.00 (0.75 to 1.33)	2019 (5 observational studies)	⨁ VERY LOW
Overall survival	HR 0.92 (0.82 to 1.03)	14,991 (9 observational studies)	⨁ VERY LOW

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number.



ACTA ONCOLOGICA
https://doi.org/10.1080/0284186X.2020.1797161

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ORIGINAL ARTICLE

Check for updates

The effect of omission of adjuvant radiotherapy after neoadjuvant chemotherapy and breast conserving surgery with a pathologic complete response

Steven F. Mandish[a], Jeremy T. Gaskins[b], Mehran B. Yusuf[a], Yomna M. Amer[c] and Harriet Eldredge-Hindy[a]

[a]Department of Radiation Oncology, University of Louisville Hospital, Louisville, KY, USA; [b]Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY, USA; [c]School of Medicine, University of Louisville, Louisville, KY, USA

ABSTRACT

Objective(s): Neoadjuvant chemotherapy (NAC) is a standard of care for locally advanced breast cancers. Adjuvant radiotherapy (RT) after NAC is an area of active research. We hypothesize overall survival (OS) is not altered by omitting RT in women with a pathologic complete response (pCR) to NAC after breast conserving survery (BCS).

Methods: Patients from the National Cancer Database who underwent NAC, BCS, and had a pCR were included. Inflammatory disease, <6 months follow up, and unknown variables were excluded. Descriptive statistics characterized the retained cohort. Logistic regression analyzed the influence of variables on the rate of RT omission. Cox proportional hazard modeling analyzed the influence of prognostic variables on OS.

ARTICLE HISTORY
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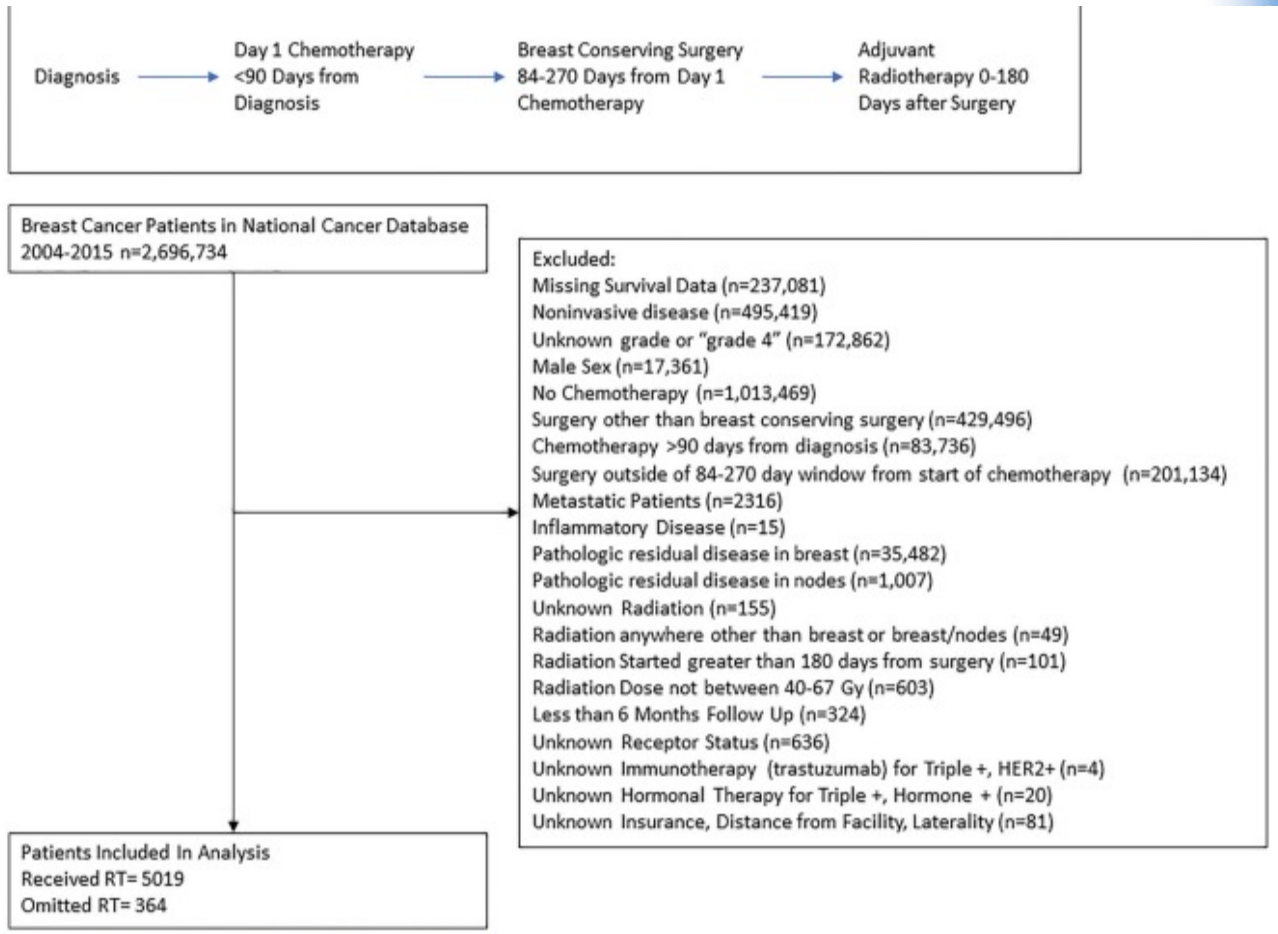

Figure 1. Timeline of patient treatment and exclusion schema.

It only reports OS data, making local, locoregional, and distant control outcomes impossible to analyze which are significant factors to consider when it comes to radiotherapy and breast cancer.

Adjuvant RT was not found to affect survival in this cohort

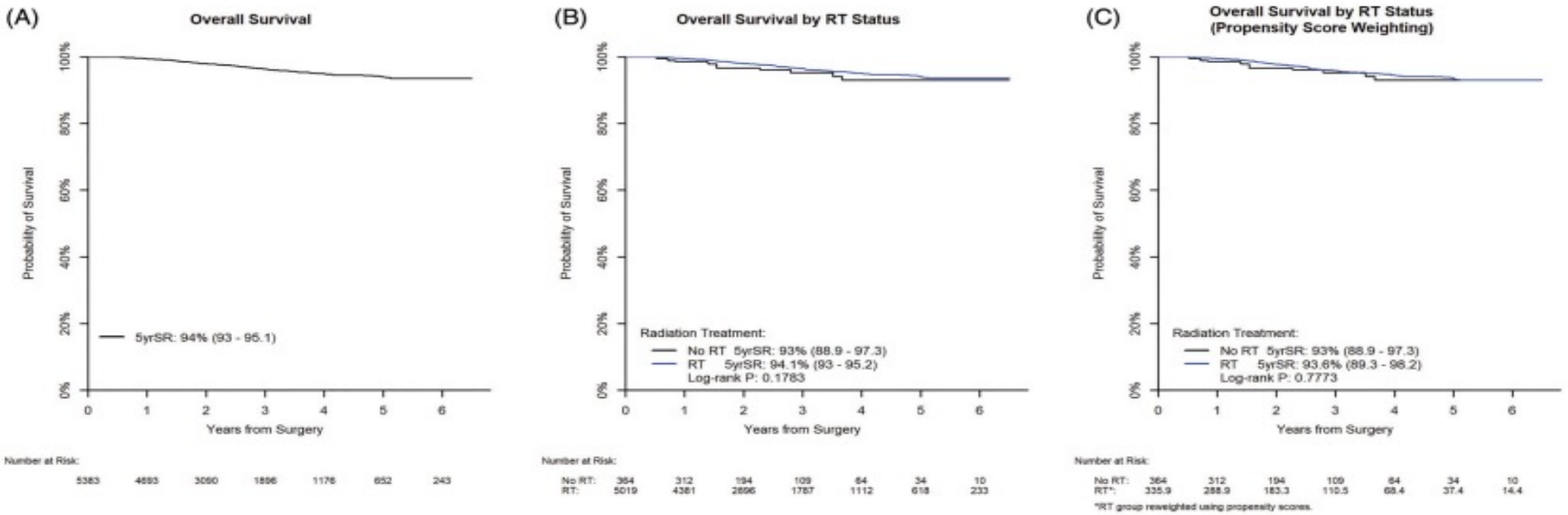

Figure 2. (A) Kaplan–Meier curve for overall survival. (B) Kaplan–Meier curve for overall survival by RT. (C) Kaplan–Meier curve for overall survival by RT propensity score weighted.

NRG Oncology/NSABP B-51/RTOG 1304: Phase III Trial Evaluating Benefit of Adjuvant Regional Nodal Irradiation in Patients With Early Breast Cancer Converting to Axillary Lymph Node Negativity After Neoadjuvant Chemotherapy

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NRG Oncology/NSABP B-51/RTOG 1304: Study Design

- Randomized, open-label phase III trial

Stratified by type of surgery (mastectomy vs lumpectomy), HR status (+/-), HER2 status (+/-), adjuvant chemotherapy (Y/N), and breast pCR status (Y/N)

Patients with **clinical T1-3, N1**, M0 breast cancer; axillary LN+ by FNA or core needle biopsy; completed ≥8 wk of neoadjuvant chemotherapy (+ anti-HER2 therapy if HER2+); ypN0 by SLNB (≥2 nodes excised), ALND, or both after neoadjuvant chemotherapy; mastectomy or lumpectomy (N = 1641)

No regional nodal irradiation (n = 821)
Breast radiation if breast-conserving surgery
No chest wall radiation if mastectomy

Regional nodal irradiation (n = 820)
Breast radiation if breast-conserving surgery
Chest wall radiation if mastectomy

- **Primary endpoint:** IBCRFI (time from randomization to invasive local, regional, or distant recurrence, or death from breast cancer)
- **Secondary endpoints:** LRRFI (locoregional recurrence without distant recurrence within 2 mo), DRFI, DFS, OS, toxicity

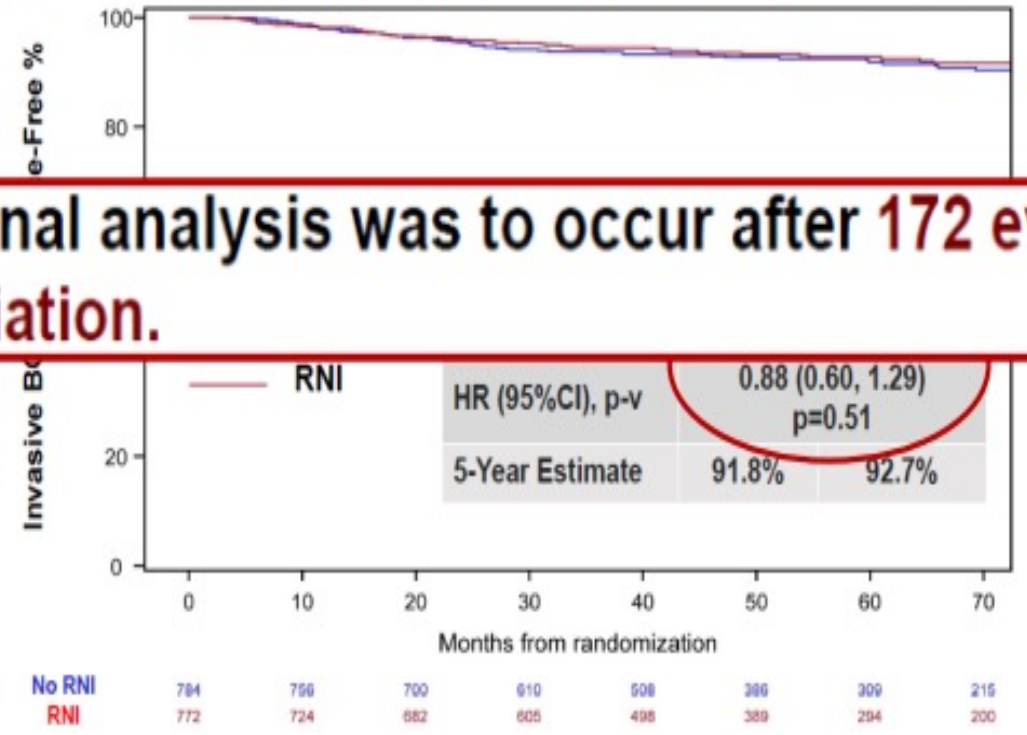
NRG Oncology/NSABP B-51/RTOG 1304: Baseline Characteristics

Characteristic	No RNI (n = 821)	RNI (n = 820)
Median age, yr (range)	52	52
Age, %		
▪ ≤49 yr	40	41
▪ 50-59 yr	32	33
▪ ≥60 yr	28	26
Race, %		
▪ White	69	69
▪ Black	17	18
▪ Asian	8	6
▪ Unknown/other	6	6
Ethnicity, %		
▪ Not Hispanic/Latino/a	83	82
▪ Hispanic/Latino/a	14	14
▪ Other	3	3
Clinical tumor size, %		
▪ T1	21	21
▪ T2	59	61
▪ T3	20	18

Characteristic, %	No RNI (n = 821)	RNI (n = 820)
Tumor subtype		
▪ TNBC	21	23
▪ ER+ and/or PgR+/HER2-	22	20
▪ ER- and PgR-/HER2+	25	24
▪ ER+ and/or PgR+/HER2+	31	33
Breast surgery		
▪ Lumpectomy	58	58
▪ Mastectomy	42	42
Axillary surgery		
▪ SLNB	55	56
▪ ALND (± SLNB)	45	44
pCR in breast		
▪ No	22	21
▪ Yes	78	79
Adjuvant chemotherapy		
▪ No	100	99
▪ Yes	<1	1

Primary Endpoint

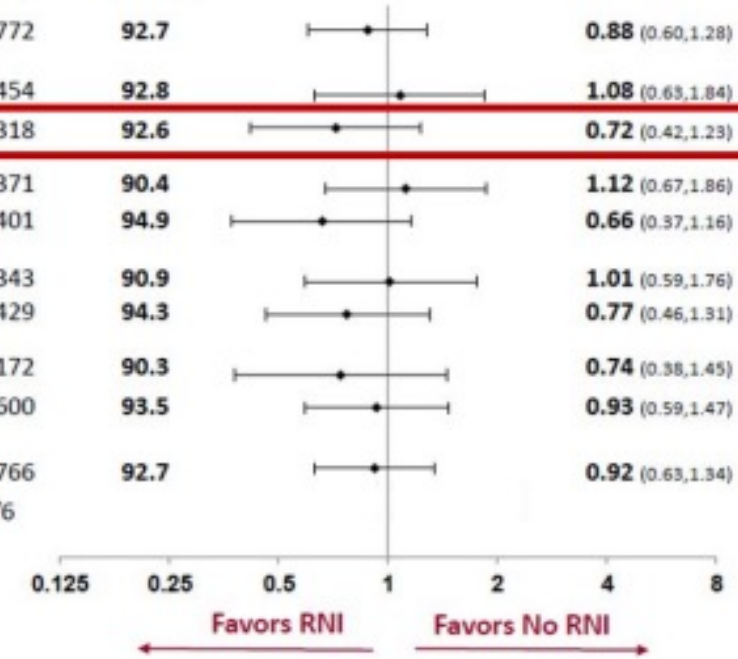
Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



Per protocol, final analysis was to occur after 172 events or 10 years after study initiation.

IBCRFI – Subgroup Analysis by Stratification Factors

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	*P*-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Surgery	Lumpectomy	26/454	**93.5**	28/454	**92.8**	**1.08** (0.63,1.84)	**0.28**
	Mastectomy	33/330	**89.5**	22/318	**92.6**	**0.72** (0.42,1.23)	
ER/PR	Negative	28/367	**91.7**	31/371	**90.4**	**1.12** (0.67,1.86)	**0.17**
	Positive	31/417	**92.1**	19/401	**94.9**	**0.66** (0.37,1.16)	
HER2	Negative	25/342	**92.6**	26/343	**90.9**	**1.01** (0.59,1.76)	**0.47**
	Positive	34/442	**91.3**	24/429	**94.3**	**0.77** (0.46,1.31)	
pCR breast	No	20/173	**87.8**	15/172	**90.3**	**0.74** (0.38,1.45)	**0.59**
	Yes	39/611	**93.0**	35/600	**93.5**	**0.93** (0.59,1.47)	
Adjuvant Chemotherapy	No	57/780	**92.1**	50/766	**92.7**	**0.92** (0.63,1.34)	
	Yes	2/4		0/6			



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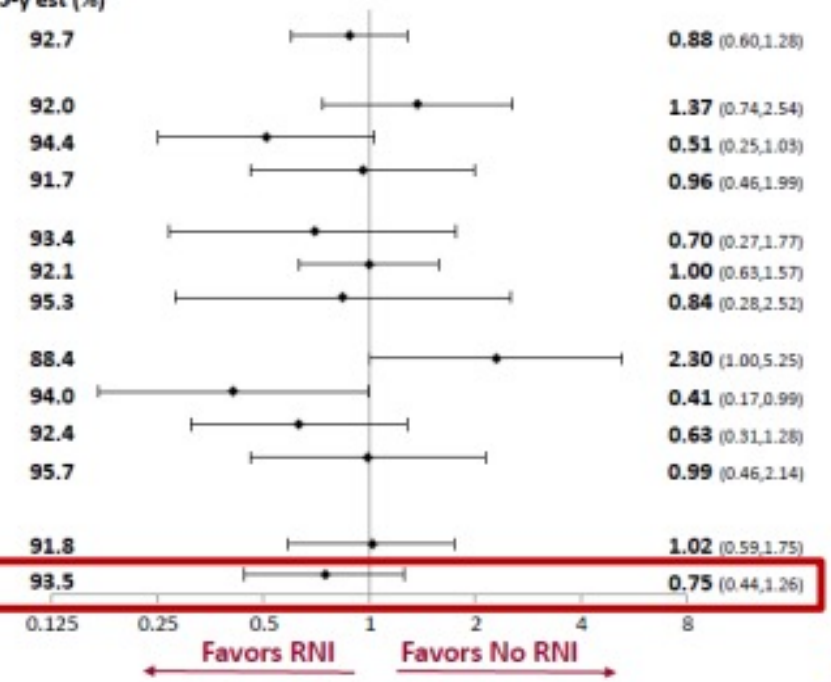
IBCRFI – Exploratory Subgroup Analysis

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	P-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Age	<=49	18/311	**92.8**	24/312	**92.0**	**1.37** (0.74,2.54)	0.09
	50-59	25/257	**90.4**	12/254	**94.4**	**0.51** (0.25,1.03)	
	>= 60	16/216	**92.4**	14/206	**91.7**	**0.96** (0.46,1.99)	
Race	Black	11/135	**92.6**	8/140	**93.4**	**0.70** (0.27,1.77)	0.69
	White	40/543	**91.6**	36/533	**92.1**	**1.00** (0.63,1.57)	
	Other	8/106	**91.8**	6/99	**95.3**	**0.84** (0.28,2.52)	
Tumor Subtype	Triple-negative	8/169	**95.0**	19/188	**88.4**	**2.30** (1.00,5.25)	0.037
	ER/PR+/HER2-	17/173	**90.5**	7/155	**94.0**	**0.41** (0.17,0.99)	
	ER/PR-/HER2+	20/198	**88.8**	12/183	**92.4**	**0.63** (0.31,1.28)	
	ER/PR+/HER2+	14/244	**93.3**	12/246	**95.7**	**0.99** (0.46,2.14)	
Axillary Surgery	Axil +/- SLNB	27/357	**92.0**	25/338	**91.8**	**1.02** (0.59,1.75)	0.42
	SLNB alone	32/427	**91.5**	25/434	**93.5**	**0.75** (0.44,1.26)	



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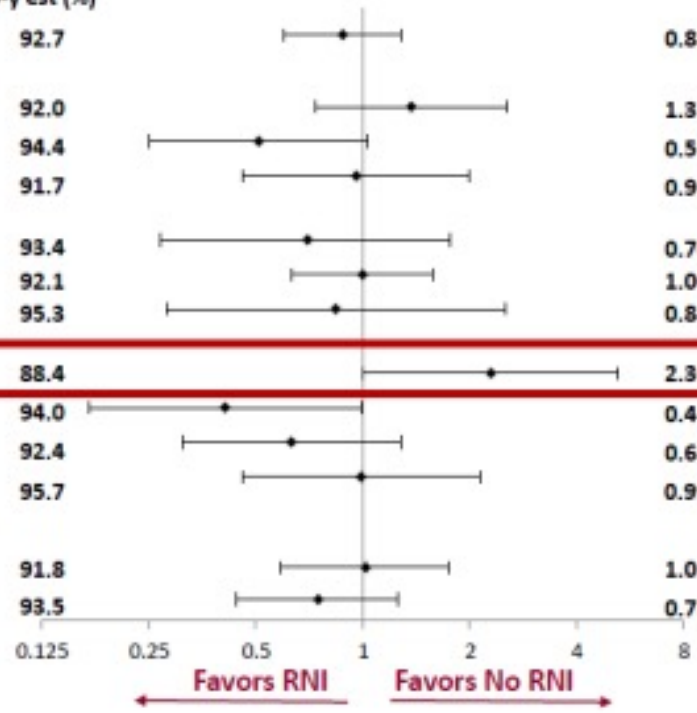
$HR_{mastectomy}$ 0.72

IBCRFI – Exploratory Subgroup Analysis

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	P-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Age	<=49	18/311	**92.8**	24/312	**92.0**	**1.37** (0.74,2.54)	0.09
	50-59	25/257	**90.4**	12/254	**94.4**	**0.51** (0.25,1.03)	
	>= 60	16/216	**92.4**	14/206	**91.7**	**0.96** (0.46,1.99)	
Race	Black	11/135	**92.6**	8/140	**93.4**	**0.70** (0.27,1.77)	0.69
	White	40/543	**91.6**	36/533	**92.1**	**1.00** (0.63,1.57)	
	Other	8/106	**91.8**	6/99	**95.3**	**0.84** (0.28,2.52)	
Tumor Subtype	Triple-negative	8/169	**95.0**	19/188	**88.4**	**2.30** (1.00,5.25)	0.037
	ER/PR+/HER2-	17/173	**90.5**	7/155	**94.0**	**0.41** (0.17,0.99)	
	ER/PR-/HER2+	20/198	**88.8**	12/183	**92.4**	**0.63** (0.31,1.28)	
	ER/PR+/HER2+	14/244	**93.3**	12/246	**95.7**	**0.99** (0.46,2.14)	
Axillary Surgery	Axil +/- SLNB	27/357	**92.0**	25/338	**91.8**	**1.02** (0.59,1.75)	0.42
	SLNB alone	32/427	**91.5**	25/434	**93.5**	**0.75** (0.44,1.26)	



Dec 5-9, 2023 SAN ANTONIO BREAST CANCER SYMPOSIUM

NRG Oncology/NSABP B-51/RTOG 1304: Efficacy

Parameter	No RNI (n = 784)	RNI (n = 772)	HR (95% CI)	*P* Value
IBCRFI events, n	59	50	0.88 (0.60-1.29)	.51
▪ 5-yr estimate of IBCRFI, %	91.8	92.7		
Isolated LRRFI events, %	11*	4†	0.37 (0.12-1.16)	.088
▪ 5-yr estimate of LRRFI, %	98.4	99.3		
DRFI events, n	48	46	1.00 (0.67-1.51)	.99
▪ 5-yr estimate of DRFI, %	93.4	93.4		
DFS events, n	83	85	1.06 (0.79-1.44)	.69
▪ 5-yr estimate of DFS, %	88.5	88.3		
	(n = 802)	(n = 800)	HR (95% CI)	*P* Value
OS events, n	45	49	1.12 (0.75-1.68)	.59
▪ 5-yr estimate of OS, %	94.0	93.6		

*2 local, 8 regional, and 1 locoregional. †All local.

- ***No significant difference in IBCRFI between arms*** for all stratification subgroups or exploratory age, race, and axillary surgery subgroups
- **Significant interaction between treatment arm and tumor subtype based on small number of events and patients** (*P* =

NRG Oncology/NSABP B-51/RTOG 1304: Safety

AE, %	No RNI (n = 800)	RNI (n = 759)
Grade 0/1	58.0	37.2
Grade 2	35.4	52.3
Grade 3	6.5	10.0
Grade 4	0.1	0.5
▪ Grade 3 radiation dermatitis	3.3	5.7

- No study-related deaths
- Toxicities were as expected

Study Schema

Clinical T1-3, N1, M0 BC

Axillary Node (+) (FNA or Core Needle Biopsy)

Neoadjuvant Chemo (+ Anti-HER2 Therapy for HER2 neu + Pts)
Path Negative Axillary Nodes at Surgery (ALND or SLNB ± ALND)

Stratification
Type of Surgery (Mastectomy, Lumpectomy); HR-status (+/–);
HER2 status (+/–); Adjuvant Chemo (yes/no); Breast pCR (yes/no)

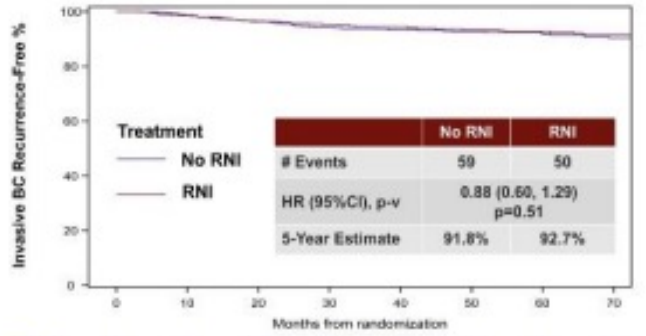
Randomization

No Regional Nodal Irradiation ("No RNI")	Regional Nodal Irradiation ("RNI")
with Breast XRT if BCS or No Chest Wall XRT if Mastectomy	with Breast XRT if BCS or Chest Wall XRT if Mastectomy

FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation

Primary Endpoint

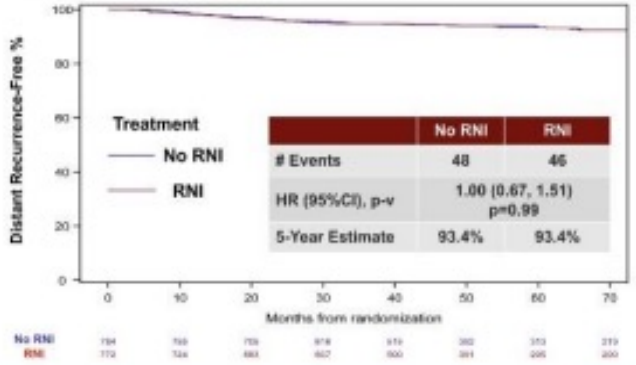
Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

Secondary Endpoints (cont.)

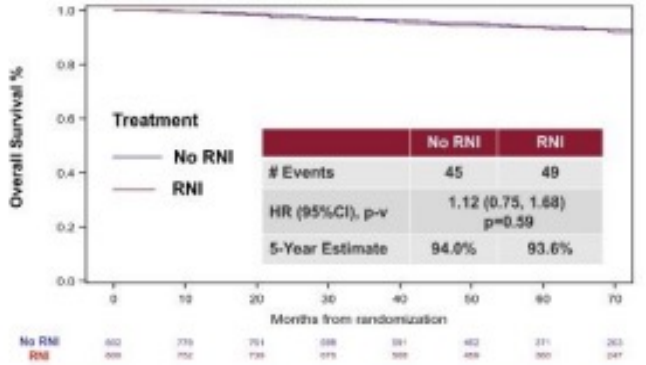
Distant Recurrence-free Interval (DRFI)



	No RNI	RNI
# Events	48	46
HR (95%CI), p-v	1.00 (0.67, 1.51) p=0.99	
5-Year Estimate	93.4%	93.4%

Secondary Endpoints (cont.)

Overall Survival (OS)



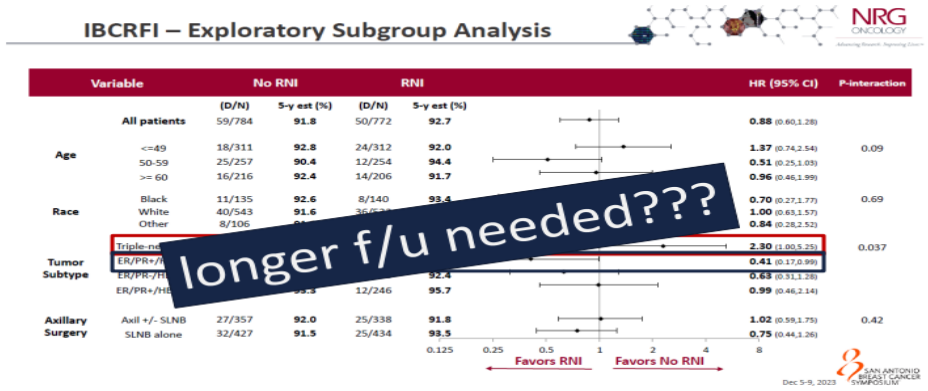
	No RNI	RNI
# Events	45	49
HR (95%CI), p-v	1.12 (0.75, 1.68) p=0.59	
5-Year Estimate	94.0%	93.6%

NRG Oncology/NSABP B-51/RTOG 1304: Investigators' Conclusions

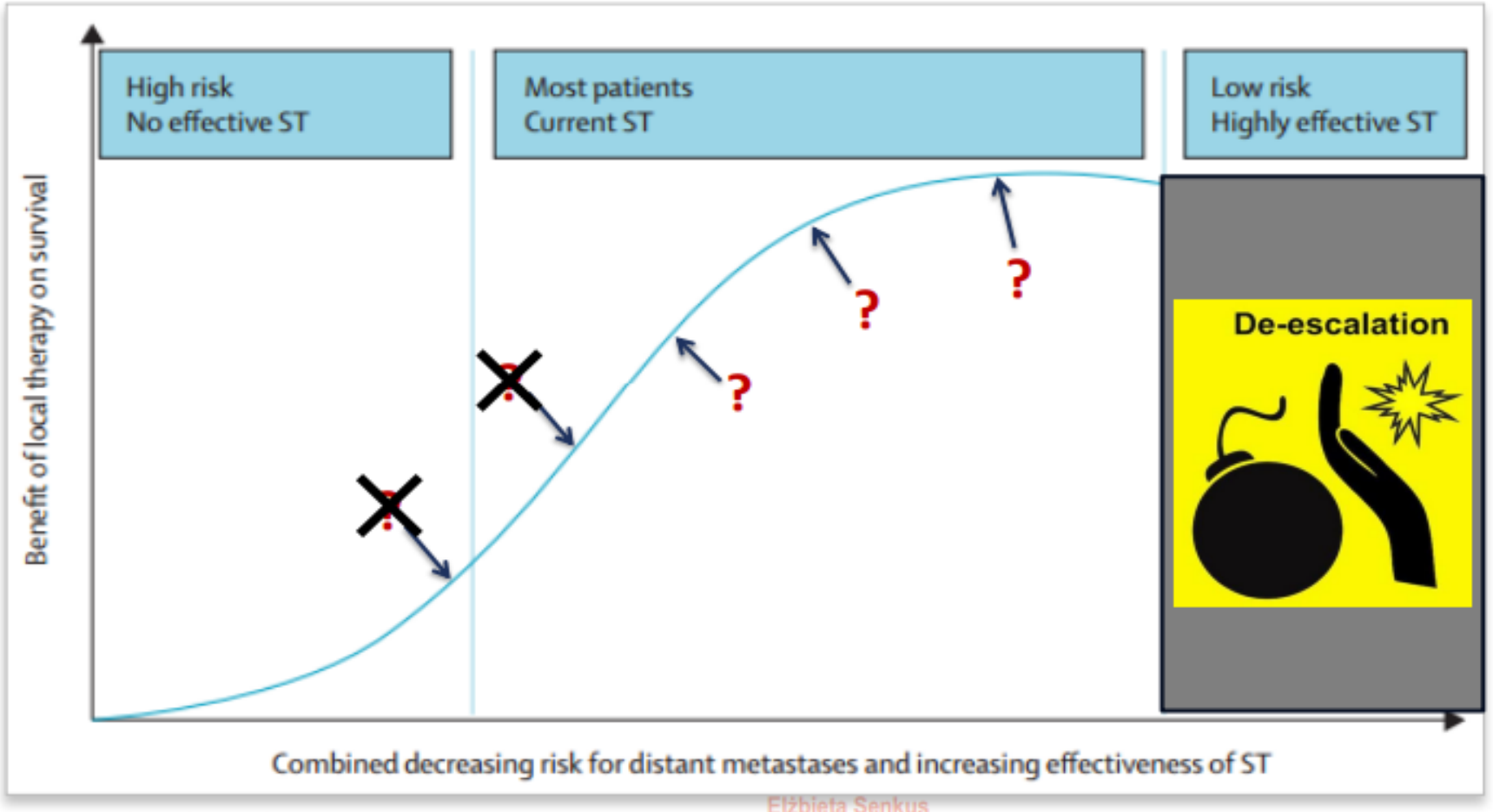
For patients with early clinically node positive breast cancer who are ypN0 after neoadjuvant chemotherapy, adjuvant regional nodal irradiation **is not associated with 5-yr IBCRFI, LRRFI, DRFI, DFS, or OS benefits**

Investigators propose that downstaging axillary nodes with neoadjuvant chemotherapy **allows for optimization of adjuvant radiotherapy without adversely affecting outcomes** propose

Long-term follow-up is ongoing



So, where are we?



When should we plan radiation in the setting of pCR based ALSO on pre-treatment assessment?

- „non-NSABP-51-like" patients
  - T_4
  - N_{2-3}
- „NSABP-51-like" patients???
  - post-mastectomy
  - post-SLNB
  - residual disease in the breast (no pCR)
  - younger age
  - less aggressive phenotypes (luminal)
  - 1 involved LN/luminal (HER2+?)

RT anyway

no RT anyway

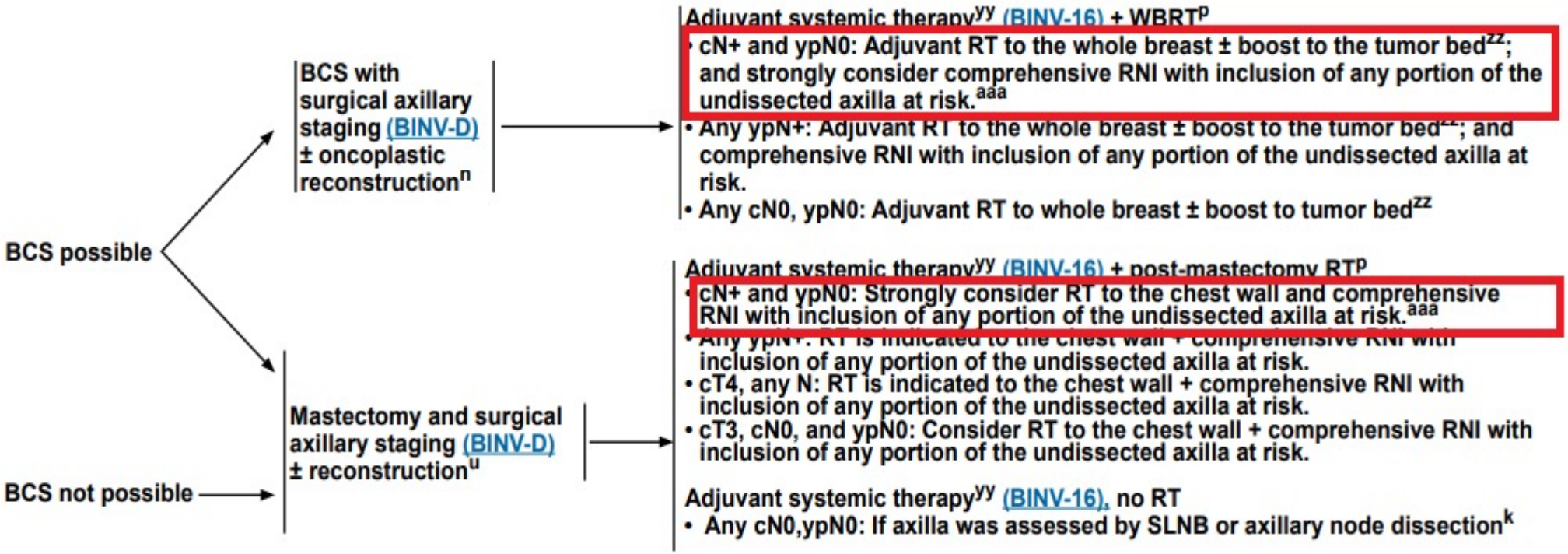
Recommendations for axillary lymph node dissection and irradiation of axillary nodal volumes in relation to pathological nodal status in cN+ patients converting to ycN0 after primary systemic therapy and sentinel lymph node biopsy /targeted axillary dissection.

	Risk group	ypN0	ypN0(i+), ypN1mi	ypN1 ≤2	ypN1 >3
PST (ChT or ET)	Low	Axillary RT: level I and II; consider RNI omission if WBI or chest wall RT	Axillary RT: level I and II	ALND, if not: axillary RT: level I and II	ALND + axillary RT: non-resected part up to level IV
	High	Axillary RT: level I-IV	Axillary RT: level I-IV	ALND + axillary RT: non-resected part up to level IV	ALND + axillary RT: non-resected part up to level IV

Risk group definition:

- Low Risk: ≤2 cN+ before PST AND complete response in the breast AND age >40
- High Risk: >2 cN+ before PST AND/OR TNBC AND/OR incomplete response in the breast AND/OR age <40.

OPERABLE DISEASE: SURGICAL TREATMENT AND ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC TREATMENT[xx]



NCCN Guidelines Version 6.2024
Invasive Breast Cancer

[n] Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction, and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS.

[p] Principles of Radiation Therapy (BINV-I).

[u] Principles of Breast Reconstruction Following Surgery (BINV-H).

[xx] The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast ultrasound and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team. MRI is more accurate than mammography for assessing tumor response to neoadjuvant therapy.

[yy] Complete planned systemic therapy regimen course if not completed preoperatively.

[zz] Strongly consider RT boost for high-risk features (eg, high-grade disease, age <50 years).

[aaa] Based on emerging data, there may be subsets of patients who achieve pCR in nodes that may not benefit from RNI (in BCS setting) or PMRT + RNI (in mastectomy setting). (Mamounas E, Bandos H, White J, et al. Loco-regional irradiation in patients with biopsy-proven axillary node Involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: Primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304; Abstract GS02-07; SABCS 2023.)

Note: All recommendations are category 2A unless otherwise indicated.

BINV-14

NCCN 2024:
RT After Preoperative Therapy and BCS

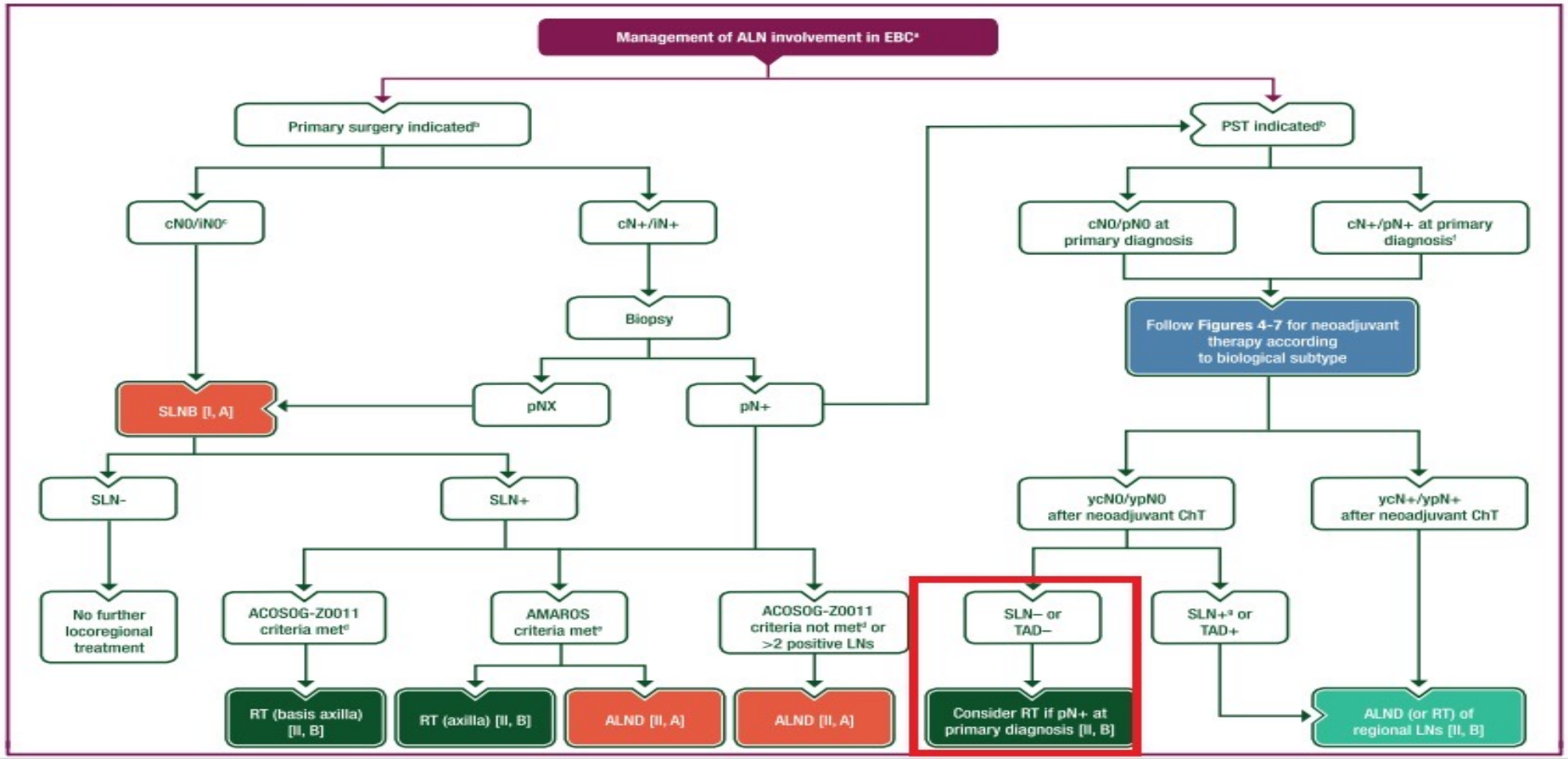
Patients who have clinically/radiographically positive nodes at diagnosis and convert to clinically/radiographically node-negative after preoperative **chemotherapy are candidates for the NSABP B-51 trial** assessing the benefit of RNI.

Until the results of this trial become available, the existing data suggest that node-positive disease at presentation is at high risk for locoregional recurrence and should be considered to receive comprehensive RNI with inclusion of any portion of the undissected axilla at risk.

NCCN 2024:
RT After Preoperative Therapy and Mastectomy

Those who have clinically positive nodes at diagnosis that respond to preoperative systemic therapy and become node-negative **should be strongly considered to receive RT to the chest wall and comprehensive RNI with inclusion of any portion of the undissected axilla**

ESMO:

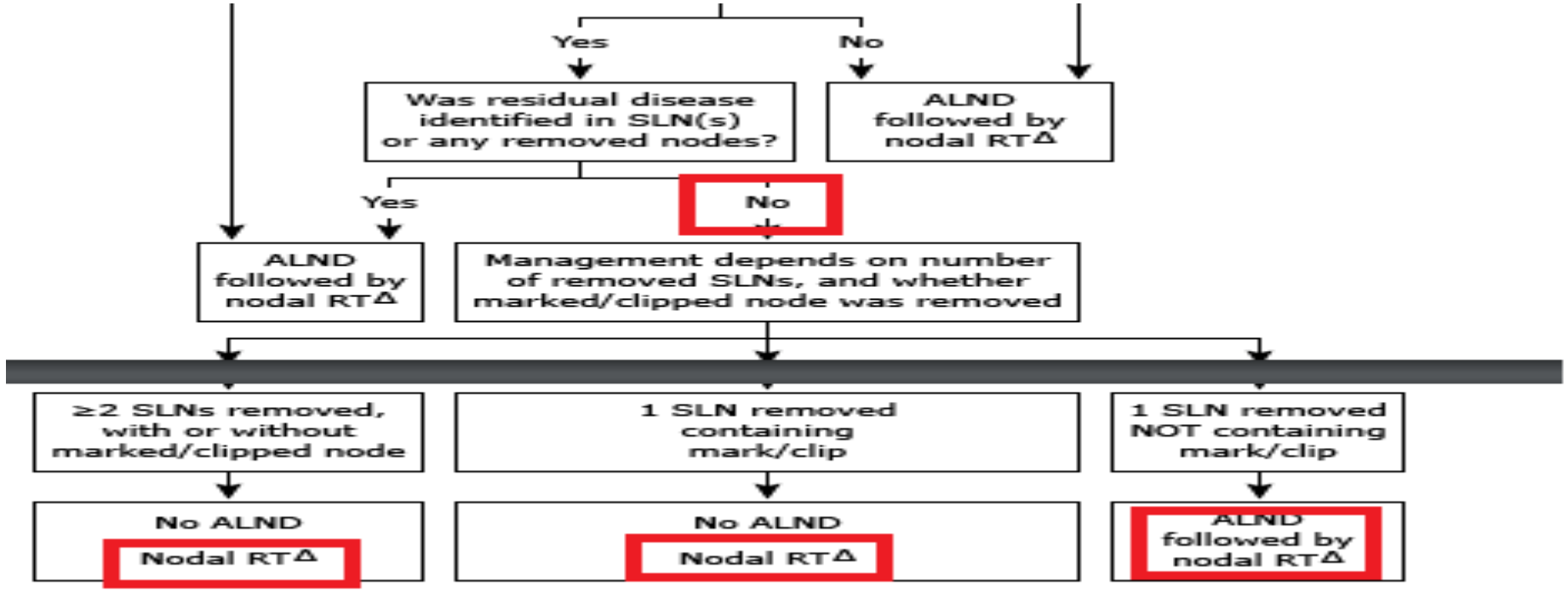

Management of ALN involvement in EBC[a]
Primary surgery indicated[b]
PST indicated[b]
cN0/iN0[c]
cN+/iN+
cN0/pN0 at primary diagnosis
cN+/pN+ at primary diagnosis[f]
Biopsy
Follow Figures 4-7 for neoadjuvant therapy according to biological subtype
SLNB [I, A]
pNX
pN+
SLN-
SLN+
ycN0/ypN0 after neoadjuvant ChT
ycN+/ypN+ after neoadjuvant ChT
No further locoregional treatment
ACOSOG-Z0011 criteria met[e]
AMAROS criteria met[e]
ACOSOG-Z0011 criteria not met[d] or >2 positive LNs
SLN– or TAD–
SLN+[a] or TAD+
RT (basis axilla) [II, B]
RT (axilla) [II, B]
ALND [II, A]
ALND [II, A]
Consider RT if pN+ at primary diagnosis [II, B]
ALND (or RT) of regional LNs [II, B]

ESMO:

In the case of PST, indications and target volumes can be individualised based on the clinical tumour stage combined with the tumour response.

Uptodate:

Δ All patients with a positive FNA or CNB of an axillary node at presentation, or one or more positive nodes after NACT, should receive regional lymph node radiation in addition to breast (if lumpectomy) or chest wall (if mastectomy) RT, unless enrolled in a clinical trial of alternative management.



In summary:

, the above-mentioned studies **strongly suggest that RNIcan be omitted in patients with cT1-2N1 (and ≤3 or less involved nodes), ypN0 (ALND) disease**,

possibly with the **exception** : of very **poor tumour biology (e.g. triple negative, no breast pCR) or very young age**. In pa tients **with stage III disease** or higher however, there is still general consensus that these will benefit from post-operative RT, regardless of their response to PST

I in patients treated with PST can be oncologically safe, if patients are adequately selected. Most studies select patients based on the 1) **cN-status: either cN0 or cN+, where some studies make a further subdivision into Low Nodal Tumour Burden (≤3 suspicious nodes at imaging) and High Nodal Tumour Burden (>3 suspicious nodes at imaging**
2**) on the ypN status, using different surgical axillary restaging procedures (SARP), i.e. SLNB and/or the removal of a marked node**

Table 1

Ongoing RCTs on de-escalating axillary treatment in patients with ypN0 disease. SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; (A)RT: (Axillary) Radiation Therapy, i.e. level 1 and 2; DFS: Disease-Free- Survival.

	Inclusion criteria	Randomization arms	Inclusion period and number of patients to include	Primary endpoint
NSABP-51/RTOG 1304 NCT01972975	cT1-3N1, ycN0, undergoing breast surgery and ypN0 (SLNB or ALND)	No additional RT (only breast RT in case of breast conservation) vs Regional Nodal RT, i.e. Level 1-4 and IMN	2013–2023 N = 1636	10-year DFS
ATNEC NCT 0410979	cT1-3N1, ycN0, undergoing breast surgery and ypN0(TAD)	No axillary treatment (No ART, and no ALND) vs Axillary treatment (ART or ALND)	2021–2030 N = 1900	5-year DFS, and 5 year Lymph-oedema of the arm


9


9