Indian College of Radiation Oncology (ICRO)

Academic Wing of

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Organising Institute

Department of Radiation Oncology
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On

"Landmark Trials & Practice Changing Evidence in Breast, H & N, GI and Gynec Cancers "

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Objectives

By the end of this presentation, you will be able to:

1. **Understand** the evolving role of regional nodal irradiation in breast cancer
2. **Analyze** key findings from pivotal clinical trials
3. **Compare** different dose fractionation schedules for nodal irradiation
4. **Apply** evidence-based decision-making algorithms in clinical practice
5. **Balance** oncologic benefits against treatment-related toxicities

Key Trials Covered

- NSABP B-51/RTOG 1304
- FAST-Forward Nodal Sub-study
- MA.20 Trial
- EORTC 22922

Current Challenges

- Patient selection for RNI
- Post-neoadjuvant management
- Optimal fractionation schedules
- Toxicity minimization

Clinical Impact

- Treatment personalization
- Resource optimization
- Quality of life considerations
- Long-term outcomes

Background & Rationale for Nodal Irradiation

Definition & Purpose

- Regional nodal irradiation (RNI) – IMN, supraclavicular, axillary nodes
- Rationale: reduce locoregional recurrence, improve DFS
- Controversy: benefit vs toxicity

High-risk Nodal Areas

- Axillary nodes (levels I–III)
- Supraclavicular nodes (SCV)
- Internal mammary nodes (IMN)

Current Controversies

- Should we give nodal RT to ypN0 after NAC?
- Conventional vs hypofractionation?
- Balancing toxicity: lymphedema, brachial plexopathy, cardiac exposure

Historical Context: Danish 82b/82c, British Columbia trials showed survival benefit from comprehensive nodal irradiation in node-positive disease.

Basics of Dose Fractionation

Fractionation Options

- **Conventional:** 50 Gy in 25 fractions (5 weeks)
- **Hypofractionation:** 40-42.5 Gy in 15-16 fractions (3 weeks)
- **Ultra-hypofractionation:** 26 Gy in 5 fractions (1 week)

Rationale for HF RNI

- Convenience & patient compliance
- Resource efficiency
- Reduced treatment burden

Barriers to Adoption

- Lack of large-scale trial evidence
- Uncertainty on late toxicity
- Technical planning challenges

Key Question: Can we extend hypofractionation from breast/chest wall to nodal volumes safely?

Overview of Key Clinical Questions

Question 1

Can we omit regional nodal irradiation in patients who achieve ypN0 after neoadjuvant chemotherapy?

Addressed by: NSABP B-51 & RTOG 1304

Question 2

Is ultra-hypofractionation safe and effective for nodal irradiation?

Addressed by: FAST-Forward Nodal Subgroup

Question 3

Does regional nodal irradiation improve outcomes in node-positive/high-risk patients?

Addressed by: MA.20 & EORTC 22922

Clinical Impact

These trials collectively inform evidence-based decision making for nodal irradiation in breast cancer, addressing patient selection, treatment volumes, and fractionation schedules.

Historical Context : Evolution of RNI

Traditional Approach

- Broad application of RNI
- Based on anatomical considerations
- Limited systemic therapy options
- One-size-fits-all approach

Modern Era Changes

- Effective systemic therapies
- Improved surgical techniques
- Molecular subtyping
- Personalized medicine approach

Key Paradigm Shifts

- **From anatomical to biological** risk assessment
- **From universal to selective** RNI application
- **From standard to hypofractionated** dose schedules
- **From disease control to quality of life** balance

Key Trials on Nodal Irradiation & Dose Fractionation

Category	Trial	Year	Population	Intervention	Primary Endpoint	Key Findings
Omission of RNI in Downstaged Patients	**NSABP B-51 / RTOG 1304**	Ongoing	ypN0 after NAC (BCS/mastectomy)	RNI vs no RNI	Invasive breast cancer recurrence-free interval	Aims to test safety of omitting RNI in downstaged patients
Hypofractionation with Nodal Coverage	**FAST-Forward (subgroup)**	2020	Early breast cancer (subset received RNI)	26 Gy/5 fx/1 week vs 40 Gy/15 fx/3 weeks	Ipsilateral breast/chest wall relapse	5 fractions non-inferior; nodal data limited but reassuring
Addition of RNI in Node-Positive or High-Risk	**MA.20**	2015	Node-positive (1–3) or high-risk node-negative, post-lumpectomy	WBI ± RNI	Disease-free survival	RNI improved DFS; ↑ toxicity; no OS benefit
Addition of RNI in Node-Positive or High-Risk	**EORTC 22922/10925**	2015; 2020 update	Node-positive or high-risk node-negative	WBI ± IMN + SCV RT	Overall survival	↓ breast cancer mortality; modest DFS gain

NSABP B-51 : Schema & Results

Study Design Details

- **Phase:** III randomized controlled trial
- **Enrollment:** 1,641 patients
- **Stratification:** Surgery type, hormone receptor status, HER2 status, adjuvant chemotherapy use
- **Eligible subtypes:** HER2+, triple-negative, or high-risk ER+ tumors

Clinical Question

Does RNI benefit patients who achieve ypN0 after neoadjuvant chemotherapy?

Population

- cT1-3, N1 breast cancer (biopsy-proven)
- HER2+, triple-negative, or high-risk ER+
- ypN0 after NAC and surgery

Randomization

- **Arm 1:** RNI (SCF ± IMN + axilla)
- **Arm 2:** No RNI (breast/chest wall only)

Key Findings (SABCS 2023)

- 1,641 patients enrolled
- Median follow-up: ~5 years
- 5-year IBCRFI: ~92% both arms
- **No significant difference**
- Lower lymphedema rates in No RNI arm

Clinical Implication :

In patients achieving pCR in axilla post NAC ,Omission of RNI appears to be oncologically safe in the short term , supporting response adapted treatment approaches

NSABP B-51 : Updated Results (2024)

Primary Results

- **Median follow-up:** 58.5 months
- **5-year IBCRFI:**
  - RNI group: 91.8%
  - No RNI group: 92.7%
  - HR: 1.10 (95% CI: 0.80-1.51), p=0.54
- **Conclusion:** No significant difference

Secondary Endpoints

- **Overall Survival:** No difference (HR: 0.83, p=0.31)
- **Distant RFI:** No difference (HR: 1.15, p=0.48)
- **Locoregional recurrence:** 2.1% vs 1.8% (p=0.60)

Toxicity Profile

- **Lymphedema (grade ≥2):**
  - RNI: 12.1%
  - No RNI: 6.3%
  - OR: 2.05 (p<0.001)
- **Grade 3+ toxicity:** Lower in no RNI arm
- **Pneumonitis:** Higher with RNI

Clinical Implication

Omission of RNI appears to be oncologically safe with significant reduction in treatment related morbidity

Citation: *Mamounas EP, et al. Omitting Regional Nodal Irradiation after Response to Neoadjuvant Chemotherapy. N Engl J Med. 2025;392(1):15-26. doi:10.1056/NEJMoa2414859*

NSABP B-51 : Case Study Applications

Case 1: Ideal Candidate for RNI Omission

Patient: 52-year-old woman

Presentation: cT2N1 triple-negative breast cancer

Treatment: Neoadjuvant chemotherapy (AC-T)

Surgery: Mastectomy + axillary lymph node dissection

Final pathology: ypT0N0 (complete pathologic response)

Decision: Omit regional nodal irradiation

Rationale: B-51 data shows no benefit of RNI in ypN0, reduces toxicity risk

Case 2: Consider Individual Factors

Patient: 35-year-old woman

Presentation: cT3N2 HER2+ breast cancer

Treatment: Neoadjuvant chemotherapy + trastuzumab

Surgery: Breast-conserving surgery + ALND

Final pathology: ypT1N0, but extensive LCIS

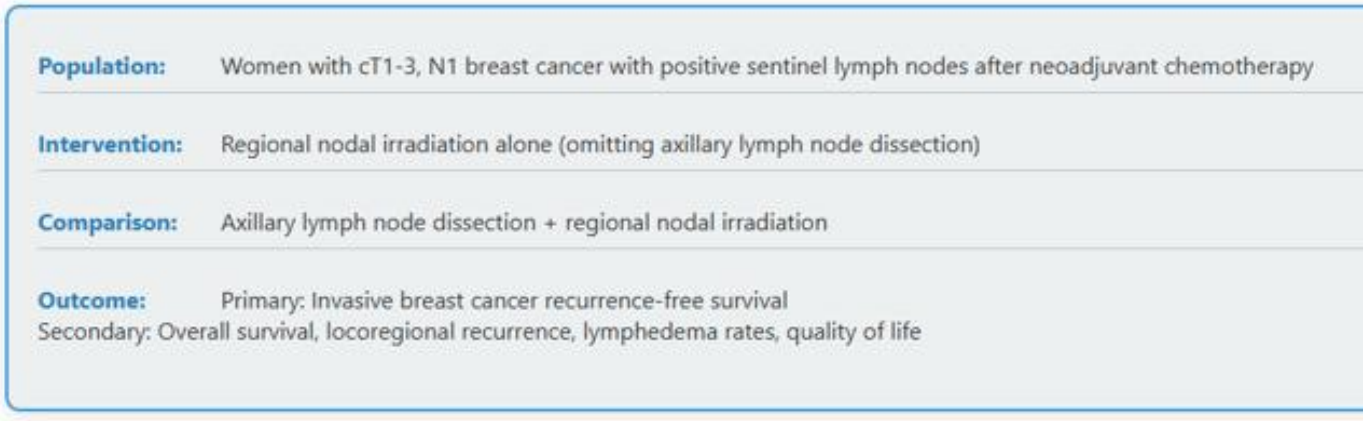
Decision: Multidisciplinary discussion

Consideration: Young age, initially bulky disease - individualize approach

Key Learning Points

- ypN0 status is the key determinant, regardless of initial nodal burden
- Tumor biology (TNBC vs HER2+ vs ER+) did not significantly affect outcomes in subgroup analysis
- Consider patient age, comorbidities, and individual risk factors
- Multidisciplinary team discussion remains important for borderline cases

RTOG 1304- Schema



Study Rationale

Whether ALND can be safely omitted in patients with residual nodal disease post NAC if comprehensive RNI is delivered

Current Status

RTOG 1304 is still ongoing with mature results pending

This complements NSABP 51 by addressing patients with residual nodal disease(ypN+) rather than ypN0

NSABP B-51 vs RTOG 1304
Response-Adapted RNI Trials

Feature	NSABP B-51 (Alliance)	RTOG 1304 (NRG Oncology)
Trial Phase & Design	Phase III, multicenter, randomized	
Population	Biopsy-proven cN1 breast cancer at diagnosis, ypN0 after NAC	Same eligibility criteria; companion study to B-51 ypN+ , Positive SLN after NAC
Intervention Arms	Arm 1: Breast/chest wall RT only Arm 2: RT + comprehensive RNI	Arm 1: Breast/chest wall RT only Arm 2: RT + comprehensive RNI (SCF, axilla, ± IMN)
Primary Endpoint	IBCRFI	IBCRFI
Secondary Endpoints	LRR, DFS, OS, toxicity, QOL	LRR, DFS, OS, toxicity, patient-reported outcomes
Stratification Factors	HR/HER2 status, breast surgery type, axillary surgery type	Same as NSABP B-51
Rationale	Address uncertainty on RNI benefit after axillary pCR post-NAC	Same rationale; confirmatory in NRG setting
Key Findings	No significant difference in IBCRFI with or without RNI	Similar: No difference in IBCRFI; Reduced toxicity in no-RNI group
Toxicity Findings	Less lymphedema, Better shoulder mobility without RNI	Same pattern; Also better PRO scores without RNI
Implications	Supports omitting RNI in ypN0 after NAC	Reinforces omission approach; supports guideline changes

MA 20 (NCIC- CTG): Schema

Clinical Question

Does adding RNI to whole breast irradiation improve outcomes in high-risk breast cancer?

Primary Endpoint

Overall Survival
Secondary: Disease-free survival, locoregional control, distant control

Study Population

- **N = 1,832 patients**
- Node-positive OR high-risk node-negative
- Post-BCS with adjuvant systemic therapy
- Enrollment: Mar 2000 - Feb 2007

Study Arms

- **Control:** WBI alone (50 Gy/25 fx)
- **Experimental:** WBI + RNI
- RNI: 50 Gy/25 fx to IMN, supraclavicular, axillary
- Well-balanced groups

Patient Characteristics

- Median age: 53-54 years
- 1 positive node: 49.5%
- 2 positive nodes: 24.1%
- ≥3 positive nodes: 16.7%
- ER-positive: 74.6%

RNI - SCLN, IMN , High Axilla

Citation: *Whelan TJ, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(4):307-16. doi:10.1056/NEJMoa1415340*

MA 20 (NCIC- CTG): Results

Primary Outcome - Overall Survival

Population	WBI + RNI	WBI Alone	HR (95% CI)	p-value
Overall Cohort	82.8%	81.8%	0.91	0.38
ER-negative	81.3%	73.9%	0.69 (0.47-1.00)	0.05

Key Results (10-year)

- **Disease-free survival:**
  - RNI: 82.0%
  - No RNI: 77.0%
  - HR: 0.76 (p=0.003)
- **Overall survival:** No significant difference (HR: 0.91, p=0.38)
- **Locoregional recurrence:** 4.3% vs 7.3% (p=0.002)
- **Distant recurrence:** 13.8% vs 17.8% (p=0.03)

No OS Benefit
Reduced Local & Distal Recurrence with RNI

⚠ Increased Toxicity with RNI

Toxicity	RNI Group	Control	p-value
Lymphedema	8.4%	4.5%	0.001
Acute Pneumonitis	1.2%	0.2%	0.01
Radiation Dermatitis	49.5%	40.1%	<0.001

Clinical Implication

Established benefit of RNI for DFS in node positive patients and high risk node negative patients with modest absolute benefit

Citation: *Whelan TJ, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(4):307-16. doi:10.1056/NEJMoa1415340*

EORTC 22922: Schema

Trial Design

- **Population:** Stage I-III with medial/central tumors or node-positive
- **Randomization:** WBI/CWI with or without IMN + SCV irradiation
- **Primary Endpoint:** Overall Survival
- **Long-term follow-up:** 15+ years

PICO Statement

Population:	Stage I-III breast cancer with medial/central tumors or node-positive disease
Intervention:	Whole breast/chest wall RT + internal mammary + supraclavicular nodal RT
Comparison:	Whole breast/chest wall RT alone
Outcome:	Primary: Overall survival

Unique Features

- First trial to show OS benefit with RNI
- Longest follow-up (20+ years)
- Included both post-mastectomy and post-BCS patients

Clinical Significance

First RCT to show OS benefit with RNI
Supporting comphrensive nodal coverage in appropriate patients

Citation: *Poortmans PM, et al. Twenty-year follow-up of the European Organisation for Research and Treatment of Cancer randomized study on regional nodal irradiation in early-stage breast cancer (EORTC 22922/10925). J Clin Oncol. 2021;39(32):3587-3597.*

EORTC 22922: Results

Key Results (15-year)

- OS: 73.1% vs 70.9% (HR 0.87)
- Reduced breast cancer mortality
- Decreased distant recurrence
- Modest but statistically significant benefit

20-year Results

- **Overall survival:**
  - RNI: 65.0%
  - No RNI: 62.2%
  - HR: 0.89 (95% CI: 0.80-1.00, p=0.055)
- **Breast cancer mortality:**
  - HR: 0.82 (95% CI: 0.72-0.94, p=0.004)
- **Disease-free survival:**
  - HR: 0.84 (95% CI: 0.76-0.94, p=0.002)

Cardiac Considerations

Increased cardiac mortality noted with older RT techniques
Modern IMRT and Breath Hold techniques significantly reduce cardiac exposure

Citation: *Poortmans PM, et al. Twenty-year follow-up of the European Organisation for Research and Treatment of Cancer randomized study on regional nodal irradiation in early-stage breast cancer (EORTC 22922/10925). J Clin Oncol. 2021;39(32):3587-3597.*

EORTC 22922: Fields used for treatment

Standard Prescription

50 Gy in 25 fractions | Patient Position: **Supine** | Gantry Rotation: **Up to 15°**

Standard IM-MS RT

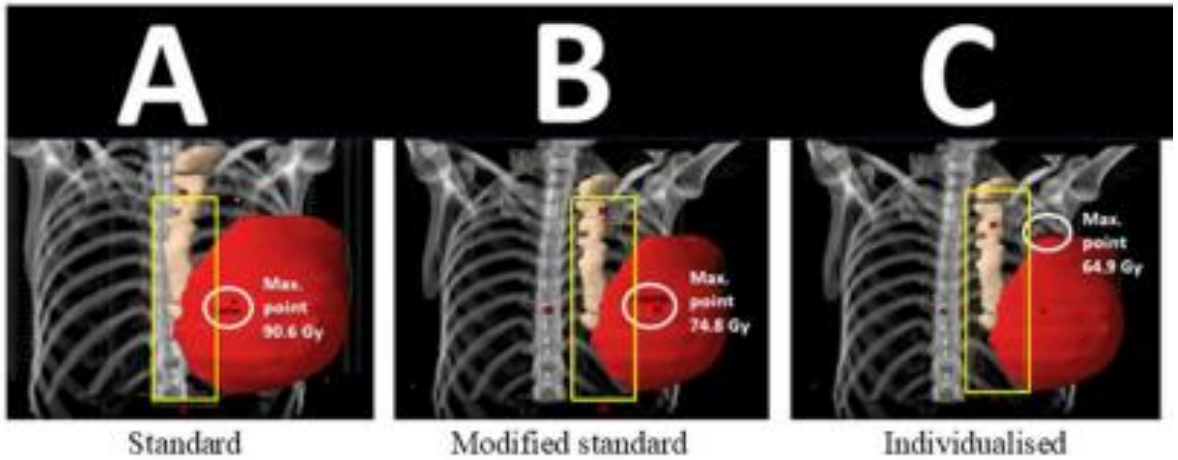
- **Mixed electron/photon:** 26 Gy photons (3cm depth, ≤10 MV) + 24 Gy electrons (100%, 12-14 MeV)
- **Target:** First 3 intercostal spaces (extend to 5th for medial lower quadrant)
- **Field size:** 6 cm wide (1 cm contralateral, 5 cm ipsilateral)
- **MS technique:** "Hockey-stick" field with blocks shielding breast overlap

Modified Standard

- **Based on:** Standard technique with minor adaptations
- **Adjustments:** Beam size, gantry angles, match line settings
- **Customization:** Electron proportion/energy based on patient anatomy
- **Approval:** Must be validated by EORTC QA team

Individualized

- **Approach:** Individual IM-node localization per patient
- **Tilburg example:** Mediolateral (IM+breast, ~1.1), Lateromedial (breast only, ~0.9), Separate IM field (~0.35)
- **Flexibility:** Custom beam shapes, energies, prescription points
- **Axillary:** Separate matched field for axillary levels



Siman-Tov, M., A. Ostrovski, M. Mast, H. Struikmans, L. Bogers, C. Fortpied, S. Hol et al. "Dosimetric Analyses of the Three Radiation Techniques Used in the EORTC 22922/10925 IM-MS Breast Cancer Trial." Clinical Oncology 36, no. 11 (2024): 690-700.
Lievens Y, Poortmans P, Van den Bogaert W. A glance on quality assurance in EORTC study 22922 evaluating techniques for internal mammary and medial supraclavicular lymph node chain irradiation in breast cancer. Radiother Oncol. 2001;60:257-65.

EORTC 22922: Complements MA 20

Study Overview
European counterpart to MA 20 with similar patient population and design

Key Similarities to MA.20

- Node-positive or high-risk patients
- Post-BCS population
- WBI ± RNI comparison
- Similar radiation techniques

Confirmatory Findings

- Improved disease-free survival
- Better locoregional control
- No overall survival benefit
- Similar toxicity profile

Combined Analysis Implications

- **Consistent results** across different populations and centers
- **Validates MA.20 findings** in European patients
- **Strengthens evidence base** for RNI recommendations
- **Confirms risk-benefit profile** across multiple studies

MA 20 / EORTC 22922: Case Study Applications

Case 3: MA.20 Application

Patient: 58-year-old postmenopausal woman

Presentation: T2N1 ER+/HER2- breast cancer

Surgery: Lumpectomy + SLNB revealing 2/3 positive nodes

Systemic therapy: AC-T + tamoxifen

Decision: Whole breast RT + RNI (IMN + SCF)

Rationale: MA.20 data supports RNI for 1-3 positive nodes

Outcome consideration: 5% absolute DFS improvement balanced against lymphedema risk

Case 4: EORTC 22922 Application

Patient: 45-year-old woman

Presentation: T3N2 central/medial tumor, ER+/HER2-

Surgery: Mastectomy + ALND (6/15 nodes positive)

Systemic therapy: Neoadjuvant chemotherapy + endocrine therapy

Decision: Chest wall + comprehensive RNI (IMN + SCF + posterior axilla)

Rationale: High nodal burden + central location - EORTC data supports survival benefit

Decision Framework Integration

- **1-3 positive nodes:** Consider RNI (MA.20 evidence) - individualize based on age, biology, comorbidities
- **≥4 positive nodes:** Strong indication for RNI (both MA.20 and EORTC support)
- **Central/medial tumors:** Consider IMN inclusion (EORTC evidence)
- **Modern techniques:** Use IMRT/VMAT with cardiac sparing (DIBH when indicated)

Fast Forward – Nodal Sub study

Population (P)

- **469 patients** from 50 UK centers
- Women/men ≥18 years with invasive breast cancer
- pT1-3, pN1-3a, M0 after complete surgical excision
- Requiring axillary radiotherapy (levels 1-4)
- Median age: 61 years (IQR: 51-70)
- 56% had axillary dissection

Intervention (I) & Comparator (C)

- **Control:** 40 Gy/15Fr over 3 weeks (n=182)
- **Test 1:** 26 Gy/5Fr over 1 week (n=183)
- **Test 2:** 27 Gy/5Fr over 1 week (n=104) - *closed early*
- All delivered with atlas-based planning and QA
- IMN radiotherapy excluded

Primary Outcome (O)

5-year patient-reported moderate or marked arm/hand swelling (EORTC QLQ-BR23)

- Non-inferiority design: exclude 10% increase (assuming 10% baseline incidence)
- 90% power, one-sided $\alpha = 0.05$, n = 172 per group
- Modified intention-to-treat analysis

469	50	76	300
Total Patients	UK Centers	Median F/U (months)	5-yr Questionnaires

FAST-Forward showed that 26 Gray (Gy) in 5 fractions (Fr) over one week adjuvant radiotherapy to breast or chest wall was as safe and effective as a three-week schedule (40 Gy/15Fr) for early breast cancer.

The nodal sub-study investigated whether a one-week schedule is safe for adjuvant axillary radiotherapy.

Applicable for Both BCS and MRM scenarios

Brunt, A. Murray, et al. "Patient-and clinician-assessed five-year normal tissue effects following one-week versus three-week axillary radiotherapy for breast cancer: Results from the phase III FAST-Forward trial randomised nodal sub-study." Radiotherapy and Oncology (2025): 110915.

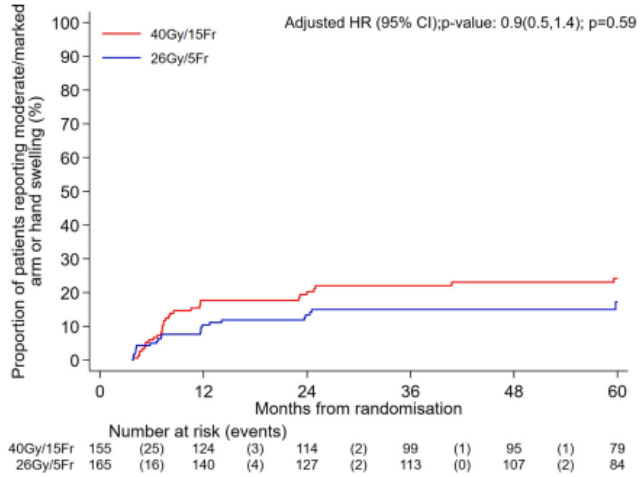
Fast Forward – Nodal Sub study

Primary Results: 5-Year Arm/Hand Swelling

Primary Endpoint Achievement

Non-inferiority demonstrated: 26 Gy/5Fr vs 40 Gy/15Fr

11% vs 10% moderate/marked swelling (Difference: 1%, 90% CI: -6%, 8%, p=0.49)



Cumulative risk of moderate or marked arm or hand swelling during follow-up by fractionation schedule (Primary endpoint)

Secondary Endpoints

Other Arm/Shoulder Symptoms (5 years)

- **Arm/shoulder pain:** 18% vs 14% (p=0.42)
- **Difficulty raising arm:** 11% vs 9% (p=0.50)
- **Shoulder stiffness:** 11% vs 9% (p=0.62)
- **Pins & needles:** 16% vs 8% (p=0.05)

No significant differences between groups

Clinician-Reported Outcomes

- **Arm lymphoedema:** 10% vs 14% (p=0.26)
- **Breast lymphoedema:** 3% vs 7% (p=0.18)
- **Brachial plexopathy:** 0% vs 0%
- **Peripheral neuropathy:** 0% vs 0%

No confirmed cases of brachial plexopathy in any group

Clinical Interpretation

- Ultra-hypofractionated nodal radiotherapy appears feasible with acceptable toxicity , but longer follow-up needed for definitive conclusions on late effect and efficacy
- Supports short course RNI in carefully selected patients ensuring compliance and optimal resource utilisation.

Brunt, A. Murray, et al. "Patient-and clinician-assessed five-year normal tissue effects following one-week versus three-week axillary radiotherapy for breast cancer: Results from the phase III FAST-Forward trial randomised nodal sub-study." Radiotherapy and Oncology (2025): 110915.

Fast Forward – Nodal Sub study

Main Conclusions

- **Non-inferiority achieved:** 5-year patient-reported normal tissue effects show 26 Gy/5Fr is as safe as 40 Gy/15Fr
- **Consistency with main trial:** Results align with FAST-Forward breast/chest wall findings
- **No brachial plexopathy:** Stringent QA measures resulted in zero cases across all groups
- **Similar symptom profiles:** Arm, shoulder, and lymphoedema rates comparable between schedules

⚠ Important Limitations

- **27 Gy/5Fr:** Higher toxicity (19% vs 10% swelling), not recommended
- **IMN radiotherapy:** Not tested - was exclusion criterion
- **Boost scheduling:** No guidance on optimal hypofractionated boost
- **10-year efficacy:** Awaiting main trial results in 2025

Future Research Directions

- **FAST-Forward Boost trial** (NIHR157800): Testing 5-fraction simultaneous integrated boost
- **IMN irradiation studies:** Investigating safety of 5-fraction IMN treatment
- **Dosimetry correlations:** Ongoing analysis of normal tissue events with dose factors
- **Long-term efficacy:** 10-year outcomes expected in 2025

Brunt, A. Murray, et al. "Patient-and clinician-assessed five-year normal tissue effects following one-week versus three-week axillary radiotherapy for breast cancer: Results from the phase III FAST-Forward trial randomised nodal sub-study." Radiotherapy and Oncology (2025): 110915.

Hypofractionation: Case Study Applications

Case 5: Standard Hypofractionation

Patient: 62-year-old woman, T2N1 disease

Surgery: Mastectomy, 1/8 nodes positive

RT recommendation: Chest wall + RNI

Fractionation choice: 40 Gy/15 fractions

Rationale: Well-established for both chest wall and nodal volumes

Technique: IMRT with heart-sparing

Case 6: Ultra-hypofractionation Consideration

Patient: 70-year-old woman, T1N1 disease

Surgery: Lumpectomy, 1/2 nodes positive

Comorbidities: Transportation challenges, COPD

RT recommendation: Whole breast + limited nodal RT

Fractionation choice: 26 Gy/5 fractions

Rationale: FAST-Forward subgroup data supports feasibility in low-risk nodal disease

Hypofractionation Selection Criteria

- **Standard HF (40 Gy/15 fx):** Well-established for most scenarios including RNI
- **Ultra-HF (26 Gy/5 fx):** Consider for:
  - Low nodal burden (1-2 nodes)
  - Older patients
  - Transportation/social challenges
  - Avoid in extensive nodal disease or young patients until more data available

Hypofractionation: Complex Case Study

Case 7: Complex Decision Making

Patient: 42-year-old woman with cT2N2 triple-negative breast cancer

Neoadjuvant therapy: AC-T with excellent clinical response

Surgery: Mastectomy + ALND

Final pathology: ypT1N1 (1/15 nodes positive, marked treatment effect)

Additional Factors

- Young age (42 years)
- Initially high nodal burden (cN2)
- Good response to NAC
- Triple-negative biology

Evidence Considerations

- **NSABP B-51:** Not applicable (patient has ypN1, not ypN0)
- **MA.20:** Supports RNI for 1-3 positive nodes
- **EORTC 22922:** Supports RNI for node-positive disease
- **FAST-Forward:** Could consider ultra-HF given low nodal burden

Recommended Approach

1. **Treatment decision:** Chest wall + RNI
2. **Rationale:** Residual nodal disease (ypN1) + young age
3. **Fractionation:** 40 Gy/15 fractions (standard hypofractionation)
4. **Volumes:** Chest wall + SCF + IMN + axilla levels I-III
5. **Technique:** IMRT with DIBH

Comparative Trial Analysis

Trial	Population	Primary Endpoint	Key Finding	NNT/NNH	Clinical Impact
NSABP B-51	ypN0 post-NAC	IBCRFI	No benefit from RNI	NNH: 17 for lymphedema	De-escalation safe
MA.20	pN+ or high-risk pN0	DFS	5% DFS improvement	NNT: 20 for DFS benefit	Supports RNI in pN+
EORTC 22922	Central/medial or pN+	OS	2.8% OS improvement	NNT: 36 for OS benefit	Long-term survival gain
FAST-Forward	Nodal subgroup	NTEC	Non-inferior toxicity	-	Supports ultra-HF feasibility

Evidence Quality Assessment

- **High quality evidence:** NSABP B-51 (recent, large, well-designed)
- **Moderate-high quality:** MA.20, EORTC 22922 (older systemic therapy era)
- **Moderate quality:** FAST-Forward nodal (subgroup analysis, limited follow-up)

Comparative Trial Analysis – Key Differences

Parameter	NSABP B-51	MA.20/EORTC	FAST-Forward
Patient Population	cN+ → ypN0 post-NACT	pN+ or high-risk pN0	pN+ requiring RNI
Primary Question	Efficacy of RNI	Efficacy of RNI	Safety of hypofractionation
Primary Endpoint	IBCRFI	Overall Survival	Normal tissue effects
Key Finding	No benefit from RNI	Improved DFS, no OS benefit	Hypofractionation safe
Clinical Impact	Omit RNI in ypN0	Consider RNI in high-risk	Shorter schedules feasible

Complementary Insights

- **Patient Selection:** Different populations need different approaches
- **Treatment Timing:** Post-NACT vs upfront surgery matters
- **Endpoint Focus:** Efficacy vs safety considerations

NSABP B-51 / RTOG 1304

ELIGIBILITY
cN1 Breast Cancer

ypN0
after Neoadjuvannt Chemo + Surgery

ARM 1
No RNI
Standard WBI ± boot / mastectomy alone

ARM 2
RNI
WBI + SCV/IMN or PMRT + RNI

5-Year IBCRFI: 92.0%
Lymphedema: 4%
Grade 3+ Toxicity: 20%

5-Year IBCRFI: 92.7%
Lymphedema: 9.1%
Grade 3+ Toxicity: 26%

PRIMARY ENDPOINT
Invasive Breast Cancer Recurrence-Free Interval

SECONDARY ENDPOINTS
OS, DFS, Locoregional Recurrence, Toxicity, QoL

FAST-FORWARD TRIAL

(UK, Phase III, n≈4096)

Early breast cancer (pT1–3, pN0–1 post-surgery)

Randomization 1:1:1

40 Gy / 15F 3 weeks

27 Gy / 5F 1 week

26 Gy / 5F 1 week

Primary endpoint
Ipsilateral breast tumor relapse at 5 years

Key results (5-year outcomes)

IBTR 2.1%	27 Gy 1.7%	26 Gy 5 F
⚠ Slightly ↑ moderate toxicity	✓ Compérble to standard, preferred	Comparablè to standard, preferred

26 Gy in 5 fractions / 1 week
Safe, effective, now a new standard

EORTC 22922 & MA.20 TRIALS

(US, Phase III, n≈4600)

Early breast cancer (pT1–3, pN0–1)

Randomization 1:1:1

WBI alone

WBI + supracla-vicular/axillary RT

Primary endpoint
Disease-free survival at 10 years

Key results

WBI alone 8.2%	WBI + regional l RT
↑ improved DFS	10-year outcomes

Evidence based Treatment Algorithm

Step 1: Assess Nodal Status Post-Treatment

- **ypN0 after NAC:** Consider omitting RNI (B-51 evidence)
- **pN+ (1-3 nodes):** Consider RNI (MA.20 evidence)
- **pN+ (≥4 nodes):** Strong indication for RNI

Step 2: Evaluate Additional Risk Factors

- **High-risk features:** Young age (<40), grade 3, LVI, close margins
- **Tumor location:** Central/medial tumors (consider IMN)
- **Biology:** TNBC, HER2+, high-risk ER+

Step 3: Select Fractionation

- **Standard:** 50 Gy/25 fx or 40 Gy/15 fx
- **Consider ultra-HF:** 26 Gy/5 fx in selected low-risk cases
- **Technique:** IMRT/VMAT with cardiac sparing

Step 4: Multidisciplinary Discussion

- **Patient factors:** Age, comorbidities, preferences
- **Social factors:** Transportation, support system
- **Shared decision-making:** Benefits vs toxicity counseling

Evidence based Treatment Algorithm for RNI - 2025

Low-Risk: Consider Omission

- ypN0 after NAC (per B-51)
- HR+/low-grade with good response
- Elderly/comorbid patients

High-Risk: Offer RNI

- ≥4 positive nodes
- 1-3 nodes + high-risk features
- Residual nodal disease post-NAC
- Aggressive biology (TNBC, HER2+)

Fractionation Approach

- **Standard:** 40-50 Gy/15-25 fx
- **Hypofractionated:** 40 Gy/15 fx (well-established)
- **Ultra-hypofractionated:** 26 Gy/5 fx (selected cases)

Special Consideration & Subgroup Analysis

🧬 Tumor Biology Matters

- **ER-negative tumors:** Greater OS benefit from RNI (MA.20)
- **HER2-positive:** Consider systemic therapy efficacy
- **Triple-negative:** Higher recurrence risk
- **Luminal A:** Lower risk, consider omission

⚠️ High-Risk Features

- T3-T4 tumors
- ≥4 positive nodes
- Close/positive margins
- Lymphovascular invasion
- Young age (<40 years)

🎯 Patient-Specific Factors

Favor RNI

- Young age
- ER-negative disease
- Multiple positive nodes
- Large tumor size
- Good performance status

Consider Omission

- Elderly patients
- Comorbidities
- Low-risk features
- Patient preference
- ypN0 after NACT

Future Directions & Ongoing Research

Ongoing Trials

- **RTOG 1304:** ALND vs RNI alone in ypN+
  - Primary completion: 2024
  - Final analysis: Expected 2026
- **NSABP B-51 extended follow-up:** 10-year outcomes
- **Dedicated HF-RNI trials:** Multiple phase II/III studies
- **Biomarker-driven studies:** ctDNA, gene expression profiles

Emerging Technologies

- MR-guided adaptive radiotherapy
- Proton therapy for nodal volumes
- AI-assisted treatment planning
- Real-time motion management

Key Research Questions

- Can we further de-escalate in excellent responders?
- Role of circulating tumor DNA in decision-making
- Optimal fractionation for different patient subgroups
- Long-term cardiac and secondary cancer risks
- Quality of life and patient-reported outcomes

Practice Evolution Timeline

- **2025-2026:** RTOG 1304 results to guide ALND decisions
- **2026-2028:** Longer B-51 follow-up and dedicated HF-RNI data
- **2028-2030:** Biomarker-driven personalization

Key Take Home Messages

Strong Evidence (Level 1)

- **ypN0 after NAC:** RNI can be safely omitted (NSABP B-51)
- **pN+ disease:** RNI improves DFS (MA.20, EORTC 22922)
- **Hypofractionation:** 40 Gy/15 fx standard for RNI

Moderate Evidence (Level 2)

- **Ultra-hypofractionation:** Feasible in selected cases (FAST-Forward)
- **Central tumors:** IMN inclusion beneficial (EORTC 22922)
- **1-3 nodes:** Individualize based on risk factors

Areas of Uncertainty

- Optimal approach for ypN+ patients (awaiting RTOG 1304)
- Long-term effects of ultra-hypofractionation
- Role of biomarkers in treatment selection
- Cost-effectiveness of different strategies

Practice Recommendations

- Use modern RT techniques (IMRT, DIBH)
- Multidisciplinary team decision-making
- Shared decision-making with patients
- Consider individual risk-benefit profile

Bottom Line

"Regional nodal irradiation should be individualized based on pathological response, nodal burden, patient factors, and contemporary evidence, with a focus on avoiding overtreatment while ensuring optimal outcomes."