Radiotherapy Exceptions After NACT/ACT

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RT after conservative surgery

- 70% decrease in local recurrence at 5 years
- 50% decrease in any first recurrence at 10 years
- 17% decrease in breast cancer mortality at 15 years

Radiotherapy after NACT in Clinically lymph node positive breast cancer

Post Neo-adjuvant Radiation Therapy in 2023

- Increasing use of NAST continues to highlight paucity of high level evidence

RT after neo-adjuvant systemic therapy

1. Debates center on relative *Importance of pre-NAST stage vs Post-NAST stage in determining LRR* risk and indications for RT

2. Does response to NAST change the risk of local-regional recurrence (LRR)?

- With improvement in pCR rates

Is it oncologically safe to de-escalate RT after pCR?

- *Importance of pre-NAST stage*

Prognostic significance of pre-NAST stage 2007

- Retrospective study of 106 patients with pCR after NAST

Pre-NAST stage	n	10-year LRR rate (%) after pCR		p
		No PMRT	PMRT	
I or II	32	0	0	
III	74	33.3	7.3	0.040

- PMRT significantly improved local-regional control, disease-specific and overall survival in stage III patients who achieved pCR after NAST
- Suggest pre-NAST tumor burden as primary determinant of post-NAST RT

McGuire et al. Int J Radiat Oncol Biol Phys 2007;68:1004-9

The Problem

cT1-T2

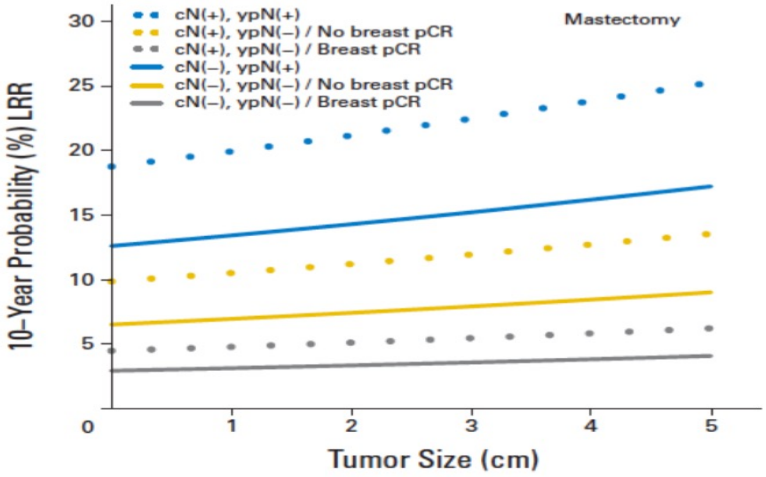
cN1

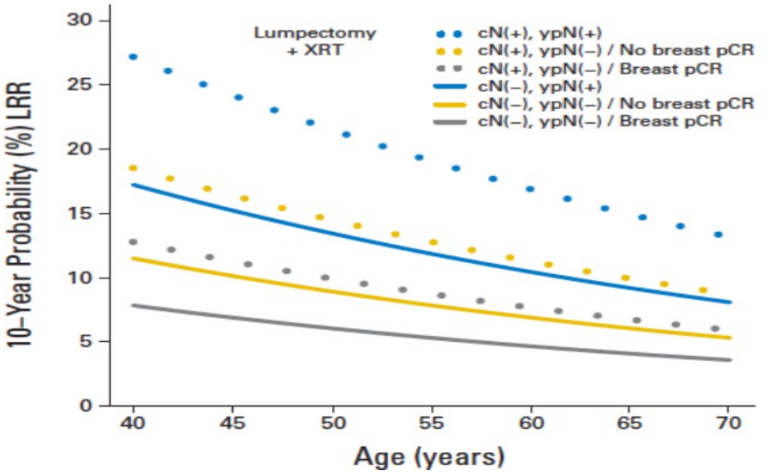
PMRT?

- *Importance of Response Rate*

Prognostic significance of post-NAST stage 2012

- Combined analysis of NSABP B-18 and B-27 in 3088 patients primarily with stage I-II breast cancer treated with NAST
- Breast RT after conservative surgery; no RT after mastectomy





Mamounas et al. J Clin Oncol 2012;30:3960-6

Prognostic significance of post-NAST stage

- 10-year LRR rates >= 15%

1. cN+/pN+
2. cN-/pN+

- 10-year LRR rates 10% -15%

1. cN+/pN- and No PCR in breast

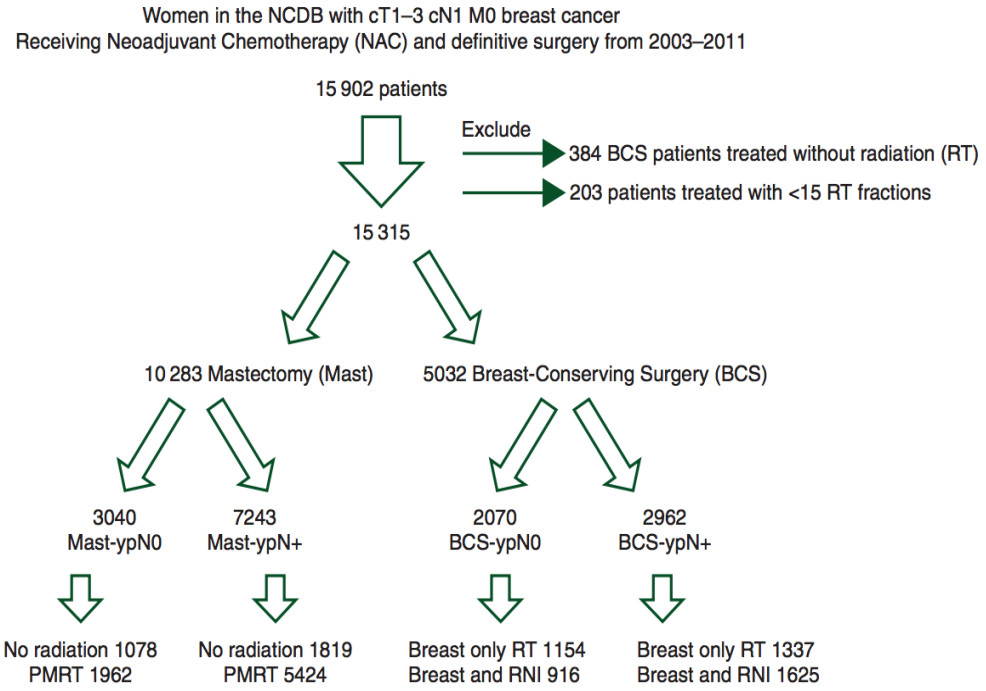
- 10-year LRR rates < 10% :

1. cN+/pN- and PCR in breast
2. cN-/pN- and No PCR in breast
3. cN-/pN- and PCR in breast

- Suggest omission of RT for ypN0 and indication for RT for ypN+

Rt in postmastectomy + ALND cN1/pN0

- Rusthoven et al*



*The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis C G Rusthoven et al. [2]Ann Oncol 2016 May

Rusthoven et al.*

- OS was improved significantly with PMRT in each pathologic nodal subgroup

(ypN0, ypN1, and ypN2-3)

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NICE review of post-mastectomy RT after NAST 2018

- 11 retrospective studies of PMRT vs no RT after NAST (n=13,565)
- Insufficient evidence to identify subgroups for omission of RT after NAST
- Decision on RT after NAST should be based on same criteria as PMRT after primary surgery including both pre and post-NAST stage

Post-mastectomy RT after NAST 2019

Pooled retrospective analysis of GeparTrio, GeparQuattro and GeparQuinto

- ✓ RT decreased LRR risk (HR 0.51, p=0.05) particularly in patients with cT3/4 primary and cN+
  - ✓ Effects of RT observed in patients converted from cN+ to ypN0 after NAST

Insufficient evidence for omission of RT after pCR

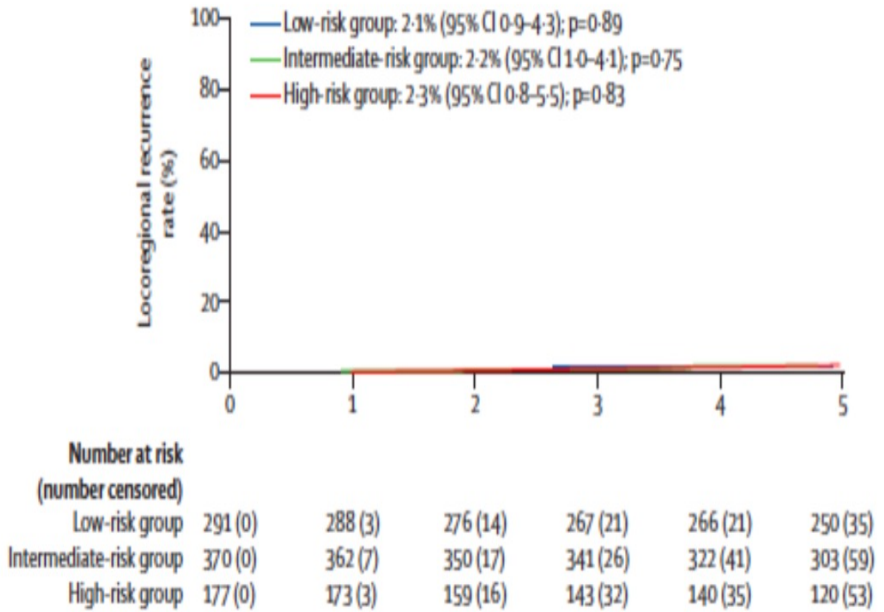
Prospective registry study of RT de-escalation after NAST (RAPCHEM; BOOG 2010-03) 2022

- To evaluate oncological safety of de-escalated RT according to predefined guidelines in patients with cT1-2 N1 breast cancer treated with NAST and surgery
- Hypothesis: 5-year LRR rate <4% (upper limit 95% CI 7.8%)

Risk group (N)	ypN	RT after lumpectomy	RT after mastectomy
Low (291)	ypN0	Breast	-
Intermediate (370)	ypN1	Breast (Axilla I-II if no ALND)	Chest wall (Axilla I-II if no ALND)
High (177)	ypN2-3	Breast + Axilla III-IV (Axilla I-II if no ALND)	Chest wall + Axilla III-IV (Axilla I-II if no ALND)

Prospective registry study of RT de-escalation after NAST (RAPCHEM; BOOG 2010-03)

- Whole group 5-year outcomes
- LRR rate 2.1% (95% CI 1.4–3.4)
- RFI 86.4% (95% CI 83.9–88.6)
- OS 92.2% (95% CI 90.2–93.8)



- Promising results for risk-adjusted de-escalation of RT in selected patients with cT1-2 N1 disease treated with NAST according to guidelines

Phase 2 trial of omitting surgery in exceptional responders to NAST 2022

- To evaluate breast RT without surgery in patients with cT1-2 N0-1 triple-negative or HER2-positive disease who had pCR after NAST determined using image-guided vacuum-assisted core biopsy

- pCR in 31/50 patients
- Median FU 26.4 months: no LR or SAE

- Suggest feasibility of RT without surgery in selected patients based on Validation required: rigorous patient selection, multidisciplinary treatment quality, response assessment, and post-treatment surveillance

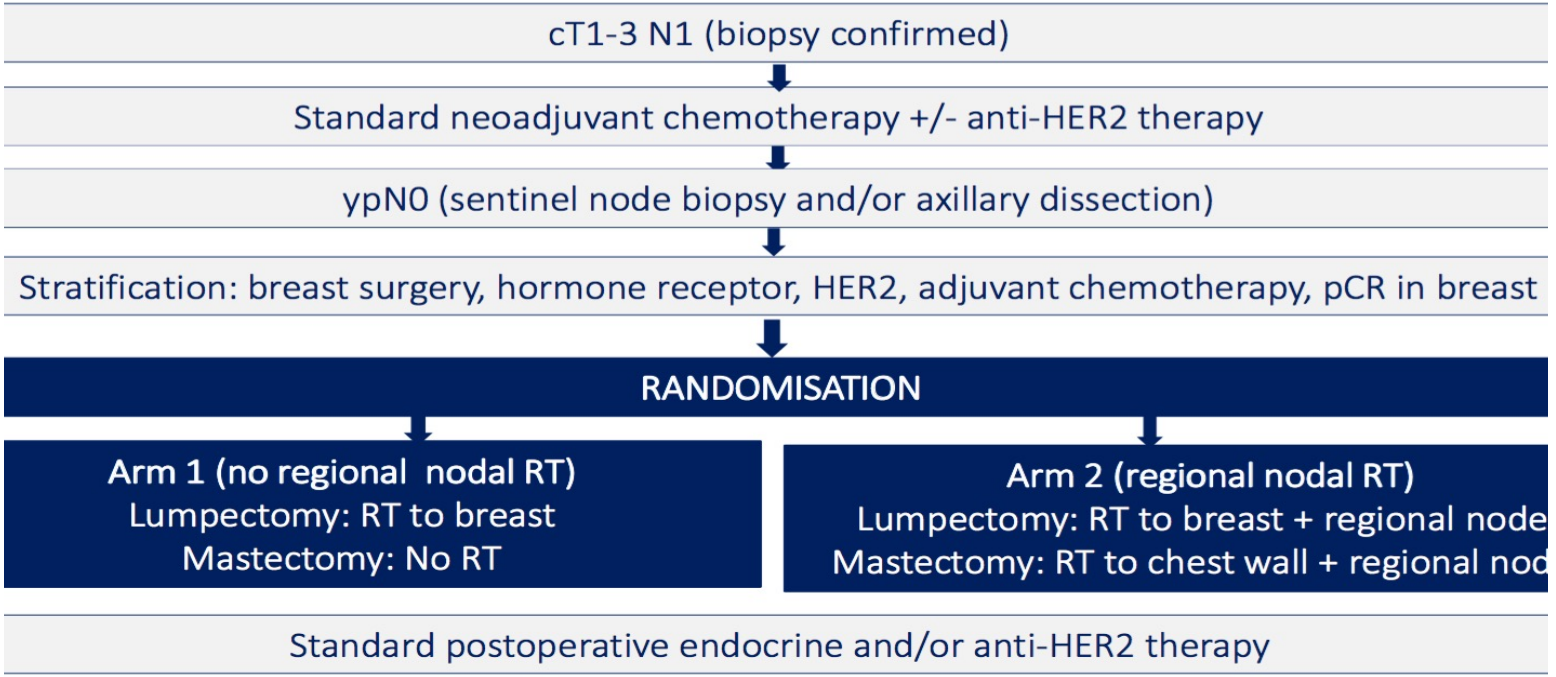
Kuerer et al. Lancet Oncol 2022:23:1517-24

Is it oncologically safe to de-escalate RT after PCR?

- Clinical equipoise on optimal local-regional therapy in patients converted from cN+ to ypN0
- RT may affect distant disease control and breast cancer mortality beyond local- regional control
- Level I evidence from randomized trials required to inform practice

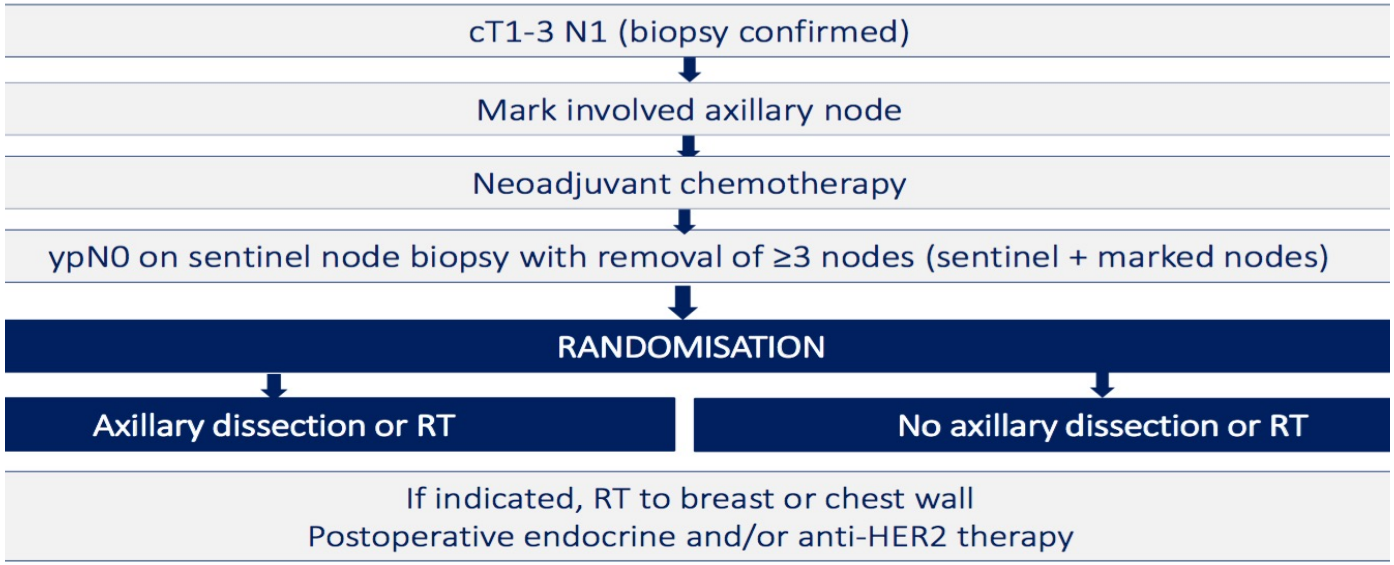
NRG Oncology Group 9353

- To assess if regional nodal RT improves invasive breast cancer RFI rate in women who are converted from cN1 disease pre-NAST to ypN0 post-NAST



ATNEC

- To assess if omitting ALND or axillary RT in patients converted from cN+ pre-NAST to ypN0 (sentinel node biopsy) after NACT is non-inferior to axillary treatment in terms of DFS, and reduces lympho-edema risk



Optimal local-regional therapy after NAST without PCR

- Patients with residual disease in sentinel nodes after NAST have>60% risk of additional nodal disease and hence, additional axillary treatment is indicated

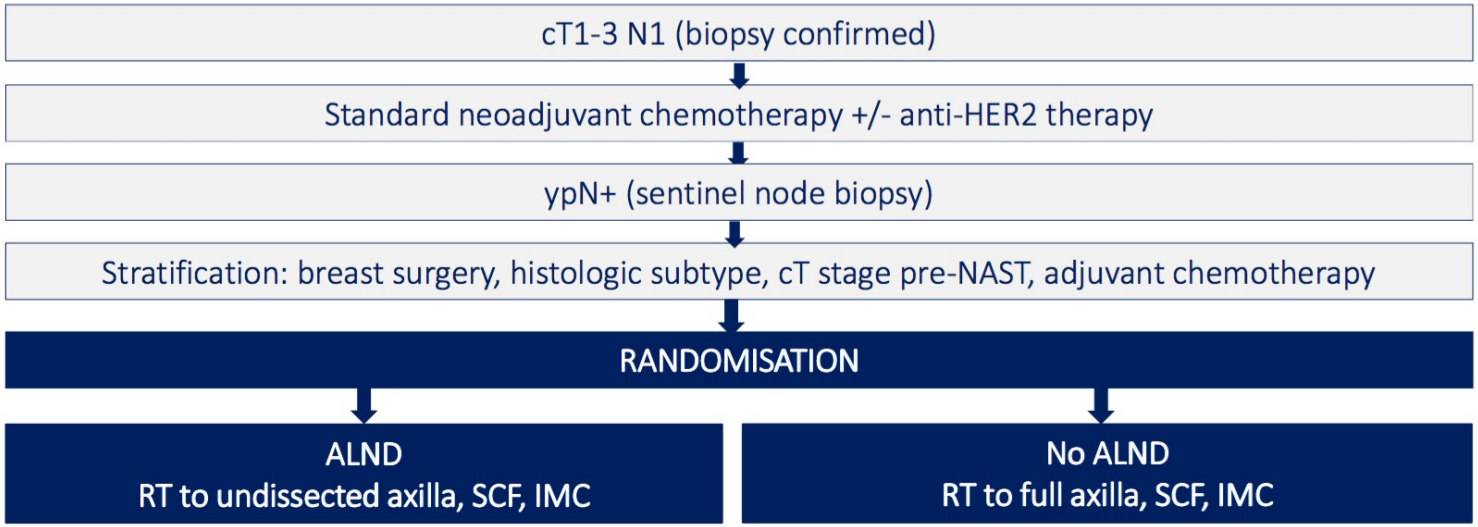
➢ *Should axillary treatment be surgery (current standard) or RT?*

- Residual disease after NAST is likely chemo-resistant

➢ *Could RT provide adequate axillary disease control without effective systemic therapy?*

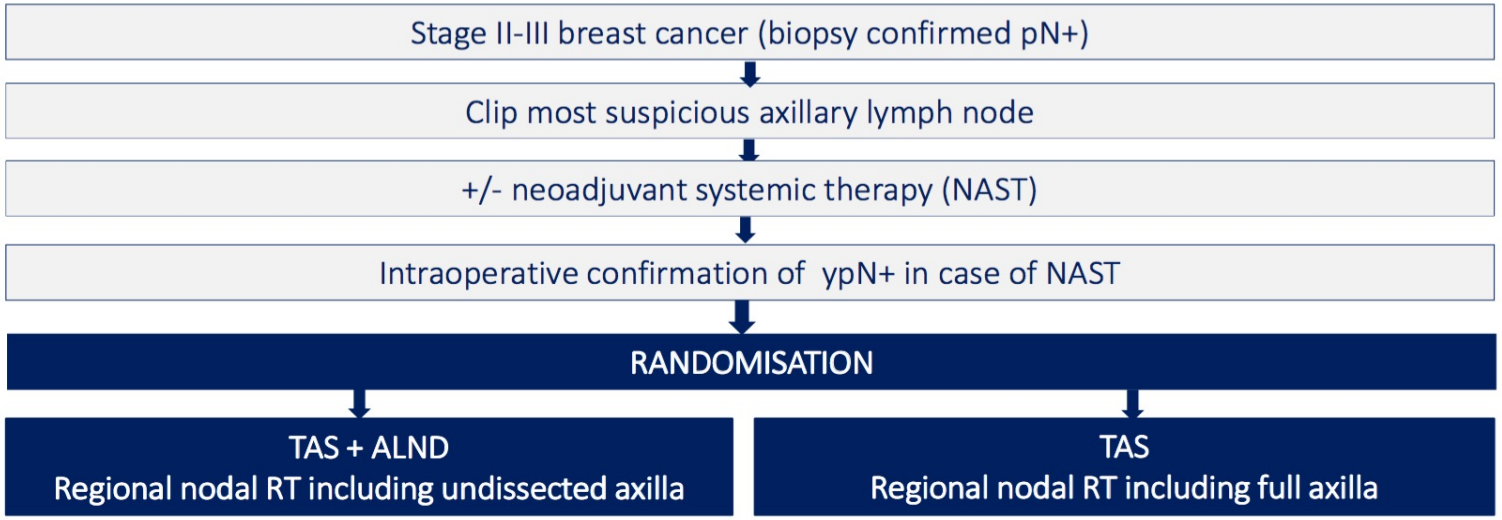
Alliance A011202

To test de-escalation of axillary surgery by replacing axillary dissection with axillary RT in patients with positive sentinel node(s) after NAST
End points: overall survival, LRR and lymphoedema rates



TAXIS (SAKK 23/16 / IBCSG 57

To examine if tailored axillary surgery (removal of clipped, sentinel and palpable nodes) and axillary RT is non-inferior to axillary dissection in terms of DFS in patients with ypN+ disease after NAST



St. Gallen Consensus Guidelines 2021

Consider both pre and post-NAST stage in RT decision

Pre-NAST	Post-NAST (SNB*)	Recommendation
cN1	ypN+	Axillary dissection (ALND)
cN1	ypN0	Regional nodal RT
cN0	ypN+ (macrometastases)	ALND
cN0	ypN+ (micrometastases or ITC)	ALND or regional nodal RT**
cT2N0	ypN0	No regional nodal RT irrespective of subtype

*Sentinel node biopsy
**Risk of residual chemo-resistant nodal metastases; ongoing clinical trials

St. Gallen Consensus Guidelines 2023

Impact of subtypes on recommendations for PMRT after NAST for cT2N+ disease% PMRT recommended

	Subtype			
Residual disease	Luminal A	Luminal B	HER2+	TNBC
Breast + nodes	78.13%	84.38%	84.38%	82.81%
Nodes	76.56%	79.37%	84.38%	84.38%
Breast	53.13%	62.50%	68.75%	73.44%
None	29.69%	32.81%	28.13%	41.54%

Conclusions

- Controversies center on relative importance of staging information pre- and post-NAST in determining LRR risk and RT decision
- Clinical trial participation to build currently limited evidence base
- Future in personalized local-regional therapy will be driven by integrating residual disease burden, tumor biology, and evolving efficacy of systemic therapy in multidisciplinary context

Radiotherapy Indication

- The decision to provide radiotherapy is currently based on The maximal disease stage (clinical stage,pathologic stage and tumor characteristics) before NAC and pathology results after NAC.

- pathologic CR does not affect the decision

Radiotherapy indication

- All patients who are undergone breast conserving surgery
- For patients who are undergone mastectomy :

cN1

cN1/pN0:SLNB + RT

cN1/pN0: ALND -/+RT*

cN1/pN+: ALND + RT

cN2/3

ALND+RT

Conclusion

- In the clinical N1 to N3 cases regardless of the response to NAC Radiotherapy is indicated

- Field of radiotherapy: In all patients WBRT/CWRT and axillary lymph node radiotherapy(controversial in cN1 patients whom ALND was done) + supraclavicular region(controversial in cN1)*

* clinical high-risk factors may influence decision(two or more of the following risk factors):

young age (≤ 40), histologic grade 3, hormone receptor negative, high proliferative index (Ki-67 ≥ 14%), and presence of LVI

Radiotherapy after Adjuvant Chemotherapy in Breast cancer

Radiotherapy Field
BCS

Primary iradiation: All patients need WBRT except

1. In patients >= 70years with T1-2N0 cancer and ER positive we can omit RT

2. PBI

- Based on ASTRO 2016 :

  Aged >= 50 years , IDC , T1,N0,free margin >= 2mm , LVI-, ER+

  DCIS <=2.5 , Grade I/II , free margin >= 3mm

- Based on NCCN :

  ASTRO criteria + negative BRCA test

Radiotherapy Field
BCS

Regional LN iradiation:

1. LN negative

consider RT in :

Central/medial tumors,pT3,pT2 with one of high risk features(GIII,extensive LVI,ER negative)

2. 1-3 positive LNs

Strongly consider comprehensive RNI

3. >= 4 positive nodes

comprehensive RNI

Radiotherapy Indication
Boost

Recommended in patients at higher risk for recurrence

(Age/margin)

Radiotherapy Indication Mastectomy

1. Chest wall irradiation:

- ✓ Tumor size >5cm (consider)
- ✓ Tumor size <= 5cm ,negative margins but <1mm (consider)
- ✓ Margin positive and re-exicionis not feasible (strongly consider)
- ✓ LN positive :1-3(strongly consider) ,>=4 (category I)

Radiotherapy Indication Mastectomy

2. Nodal Irradiation

✓ LN negative:

- In patients with T2 but free margin <1mm with high risk features Central /medial tumors or T2 with at least one of the following Grade III,LVI positive ,ER negative (consider)
- In patients with tumor size <= 5cm but free margin > 1mm (contravertial)

✓ LN positive:

- 1-3 LNs (strongly consider)
- >= 4 LNs (category I)

Radiotherapy Indication Mastectomy

- New indications

" May be considered"

Central /medial tumors or **T2** with at least one of the following:

Grade III,LVI positive,ER negative

Radiation Schedules

- ✓ Conventional Radiotherapy

  2Gy/f

- ✓ Hypofractionated Radiotherapy

  40-42.5 Gy in 15-16 f (250-266 CGy/f)

- ✓ Ultrahypofractionated Radiotherapy

  28.5 Gy/5f (once a week based on FAST Trial)

  26 Gy/5f (over 1 week based on FAST Forward Trial)

Radiation Schedules

- Chest wall RT dose: 45-50.4/25-28f (alternatively Hypofractionated if patients not undergoing breast reconstruction)
- Whole breast RT dose :40-42.5/15-16f (In selected patients conventional fractions may be considered)
- Regional node RT dose: 45-50.4/25-28f (alternatively Hypofractionated if patients not undergoing breast reconstruction)
- Ultrahypofractionated Radiotherapy may be considered for selected patients :

✓ Over 50 yrs , BCS, early stage , node negative disease , particularly those in whom a boost is not intended (based on FAST Trial)

✓ Over 18 yrs ,T1-T3 , N0-N1 , BCS or Mastectomy (based on FAST FORWARD Trial)

- FAST Trial (2020,July)

915 patients from 2004-2007,at 10 yrs fallow up there was no significant difference in side effects and local control.

- FAST FORWARD Trial (2020,April)

4096 patients from 2011-2014, at 5 yrs fallow up there was no significant difference in side effects and local control.

Thanks for your attention