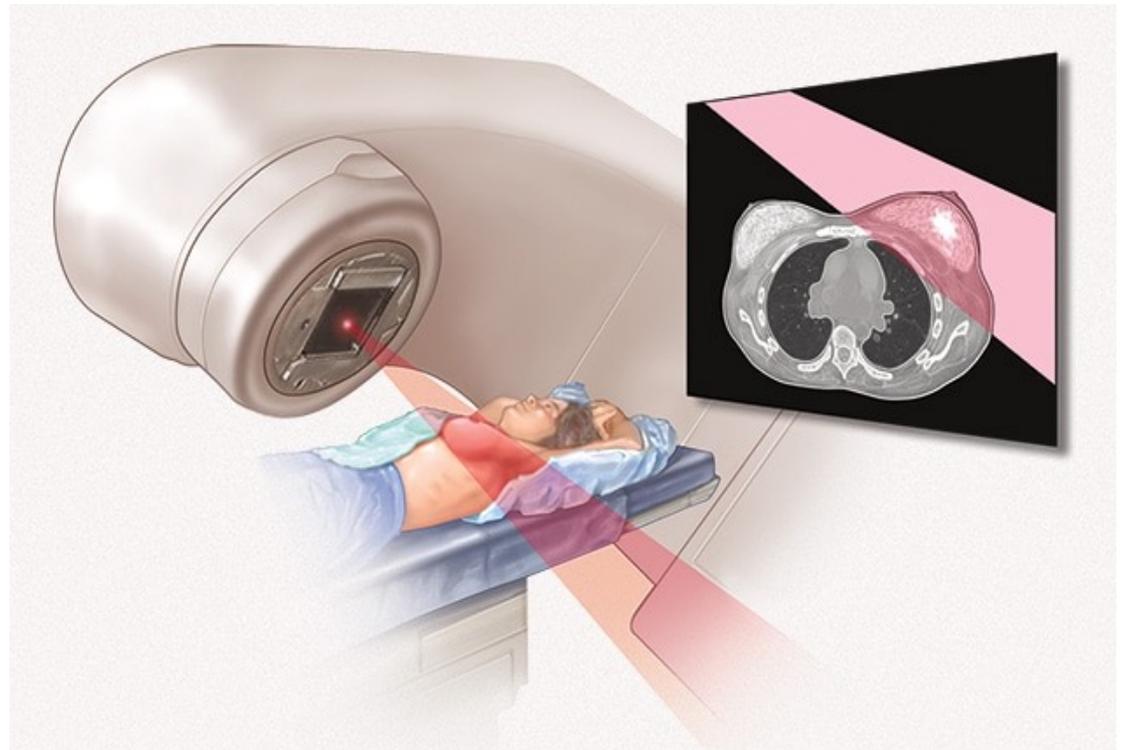


# Updates in Breast Cancer Radiotherapy

*Dr Shiva Moghadam*  
*Radio Oncologist, MCh*

- Radiation therapy (RT) remains an essential part of complex breast cancer therapy.

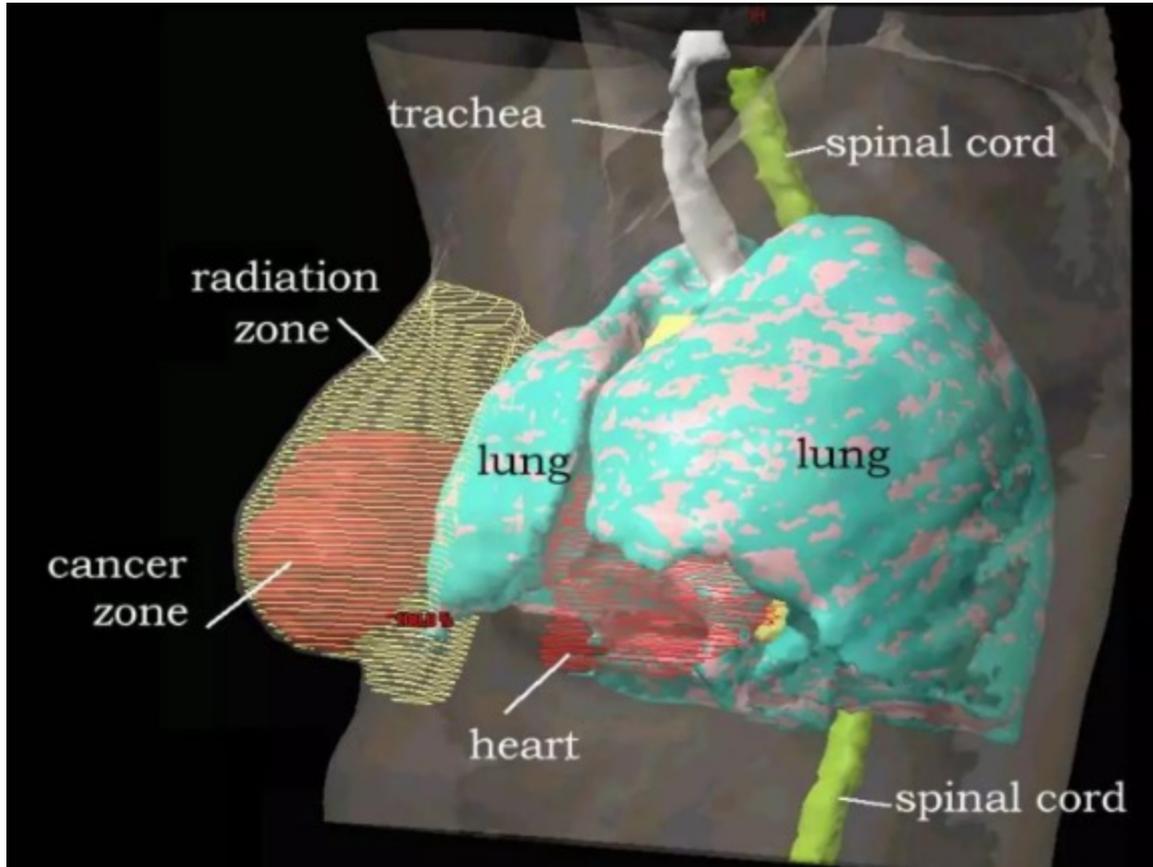
Surgery  
Chemotherapy  
**Radiotherapy**  
Hormon therapy  
Target Therapy  
...



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- ✓ RT after BCS is indicated in ductal carcinoma insitu (stage 0), since it decreases the risk of local recurrence (LR) by 50–60% .
- ✓ In early stage (stage I-II) invasive breast cancer RT remains a standard treatment following BCS.
- ✓ Following mastectomy, RT significantly decreases the risk of LR and improves overall survival of patients who have 1 to 3 (pN1a) or  $\geq 4$  positive axillary lymph nodes.
- ✓ According to the latest randomized trials (EORTC 22922/10925 and NCIC-CTG MA.20), regional RT significantly improves both disease-free and distant metastasis-free survival, while its effects on overall survival are contradictory.

- ✓ In all indications (DCIS, invasive breast cancer and regional irradiation) intensive research is in progress to predict the benefit of RT using various molecular markers with the aim of deescalating therapy in low-risk cases that do not require RT.
- ✓ After neoadjuvant systemic treatment (NST) followed by BCS, WBI is mandatory, while after NST followed by mastectomy, postoperative RT should be given in cases of initial stage III–IV and  $\geq$ ypN1 axillary status.



## Ductal Carcinoma In situ

- Irradiation is usually recommended after BCS because 50 Gy administered to the residual breast decreases the risk of local recurrence by 50%–60% in all risk groups (recommendation category: 1)
- Usually, 50% of local relapses are DCIS and the other 50% are invasive cancer.
- For low-risk patients (well-differentiated lesion, with minimal or no necrosis, at least 10 mm safety zone, >65 years of age) radiation therapy may be omitted based on individual assessment (recommendation : 3)
- Partial breast irradiation for DCIS can only be administered in the framework of a prospective clinical trial (recommendation : 3)

## Ductal Carcinoma In situ

- Chest wall RT is not required after mastectomy (recommendation 2A).
- Irradiation of lymphatic regions is not justified: pTis N0 M0 (recommendation: 2A).
- In cases of Paget's disease of the nipple, wide cone excision should be followed by RT of the residual breast (recommendation category: 1).

## IDC: BCS Followed by Irradiation of the Residual Breast Tissue

- Irradiation of the residual breast decreases the risk of local recurrence by 75% in all age groups.(1)
- RT also significantly improves the 15-year breast cancer-specific survival—by 5% and 7% in patients with negative or positive lymph nodes, respectively.
- For older ( $\geq 70$  years of age) patients with good prognosis (stage I, negative surgical margin, hormone receptor-positive tumour) discontinuing RT and using only endocrine therapy can be considered—with the informed consent of the patient—since RT does not improve 10-year OS, but the patient must be fully informed of the significantly higher risk of local recurrence at 10 years and its consequences (2a)
- Treatment of the tumour bed with elevated (“boost”) dose improves local tumour control in all risk groups, but for very low-risk patients the absolute benefit of this treatment is limited ( $\leq 3\%$  at 20-year follow-up).(1)

## IDC: Chest Wall Irradiation After Mastectomy

- **pT1-2 pN0-1mi**: Irradiation is not needed if the tumour was resected with intact surgical margins (1). Although chest wall irradiation slightly decreases the rate of local recurrence at 5 years (from 1.9% to 1.2%), it does not improve breast cancer-specific survival. According to the NCCN protocol, chest wall irradiation should be considered if the intact surgical margin is  $\leq 1$ mm.
- **pT3 pN0**: Chest wall irradiation is recommended (2a)
- **pT1-2 pN1a-2a-3a**: Locoregional RT is recommended (1)  
RT decreases the incidence of local recurrences at 5 years by  $\sim 15\%$  (1–3 positive lymph nodes: from 17% to 3%, 4 or more positive lymph nodes: from 26% to 11%) and improves 20-year breast cancer-specific survival by 8–10%.
- **pT1-2 pNx or pN0 but <6 examined lymph nodes** (except when sentinel lymph node biopsy was performed): irradiation should be considered (2b).

## **Immediate breast reconstruction following mastectomy:**

the reconstructed breast and the chest wall are treated according to the above guidelines. The two-stage procedure provides a better result than immediate reconstruction with implant: expander insertion, irradiation of the expander, and after the irradiation the expander is replaced with the permanent implant.

## IDC: Sentinel Lymph Node Biopsy Followed by Irradiation

**pN0-1mi (sn):** If the sentinel node (SN) is negative or if there is a micrometastasis, usually there is no need for nodal irradiation (recommendation category: 2a).

**but** irradiation of **axilla levels 1–2 should be considered** if there is an increased risk: (histology indicated an aggressive tumor, >pT1, multifocality, presence of LVI, a single SN was removed, systemic therapy is anticipated to have low or no efficacy, young age of the patient) (3).

## IDC: Sentinel Lymph Node Biopsy Followed by Irradiation

- **pN1a (sn):**
  - ✓ If there is a macrometastasis (>2 mm) in the sentinel lymph node and **axillary dissection** is performed, then RT of the supraclavicular region (level 4) and axillary apex (level 3) is recommended, while there is no need to irradiate levels 1–2 (2a).
  - ✓ If **no axillary dissection** is performed (according to ACOSOG Z011 criteria), then irradiation of the axillary lymph nodes and, based on individual risk, other regional lymph nodes is required, since an incidence of metastases of 27–38% is estimated in the non-dissected non-sentinel lymph nodes (2b)

**Generally levels 1–3 of the axilla and SC are irradiated (2a), but in the presence of lower risk it is sufficient to irradiate levels 1–2 of the axilla (favourable histology, pT1, unifocality, only one of several sentinel lymph nodes is involved, size of macrometastasis is <7 mm, effective systemic therapy, relatively older patient (3).**

## Axillary Lymphadenectomy Followed by Irradiation

- **pN0-1mi:** RT is not necessary (1).
- **pN1a, 2a, 3a, N3c :**
  - RT of the supraclavicular region and axillary apex is recommended (2a).
  - If there has been adequate axillary dissection ( $\geq 6$  lymph nodes) for N1a the use of elective supraclavicular field is sufficient, while irradiation of levels 1–2 is not required (2a).
- **pNx or pN0 but <6 examined lymph nodes (except when sentinel lymph node biopsy was performed):**
  - After inadequate lymphadenectomy RT of the supraclavicular and axillary region (levels 2–3) is recommended based on individual consideration.

## Axillary Lymphadenectomy Followed by Irradiation

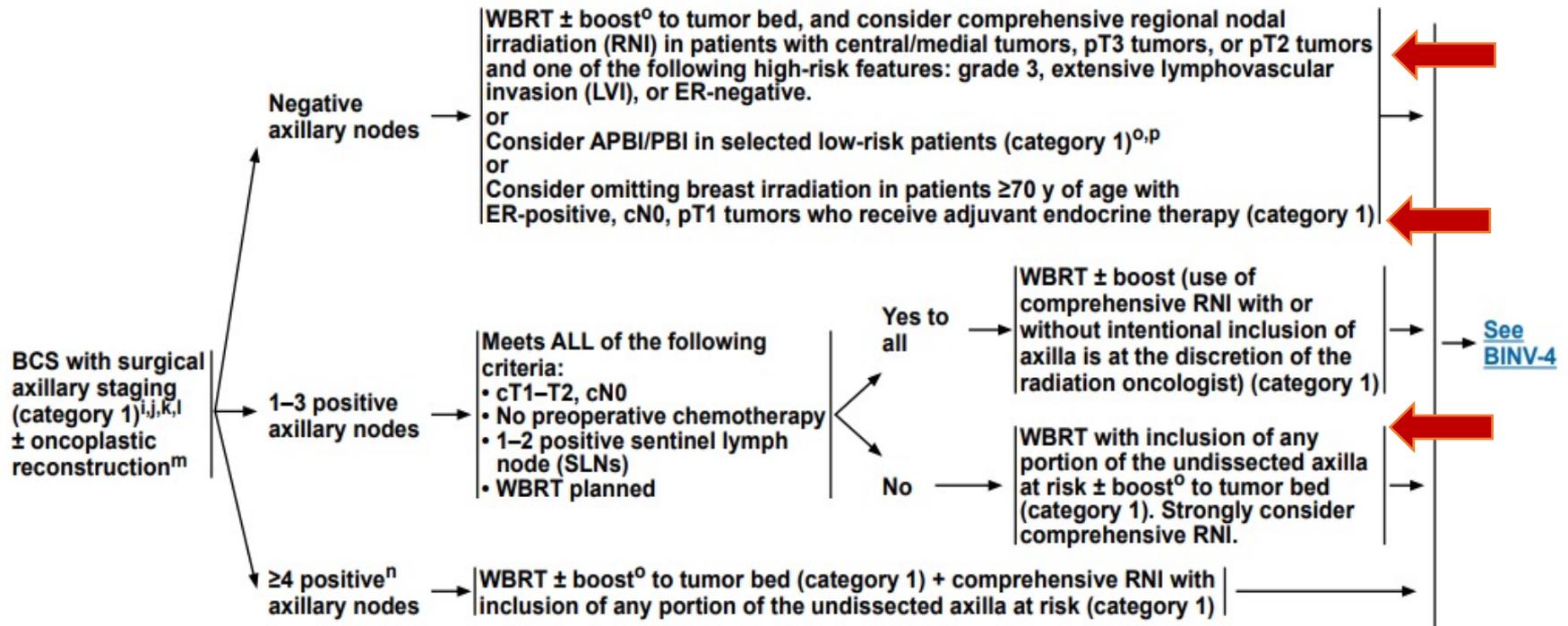
### For parasternal lymph nodes radiation:

- ✓ professionals should always consider the risks of lung and heart exposure.
- ✓ As clinical manifestation of parasternal lymph node recurrence is very rare (<1%) and according to the latest published studies the role of parasternal lymph node irradiation in improving overall survival is not fully clarified, hence the routine elective RT of this region is still controversial (3)
- ✓ If there is histologically confirmed internal mammary sentinel lymph node or clinically unequivocal (CT, US, MRI) parasternal lymph node metastasis, irradiation is recommended even in the presence of negative axillary status (2a).



## LOCOREGIONAL TREATMENT OF cT1-3, cN0 or cN+, M0 DISEASE:<sup>a</sup> BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

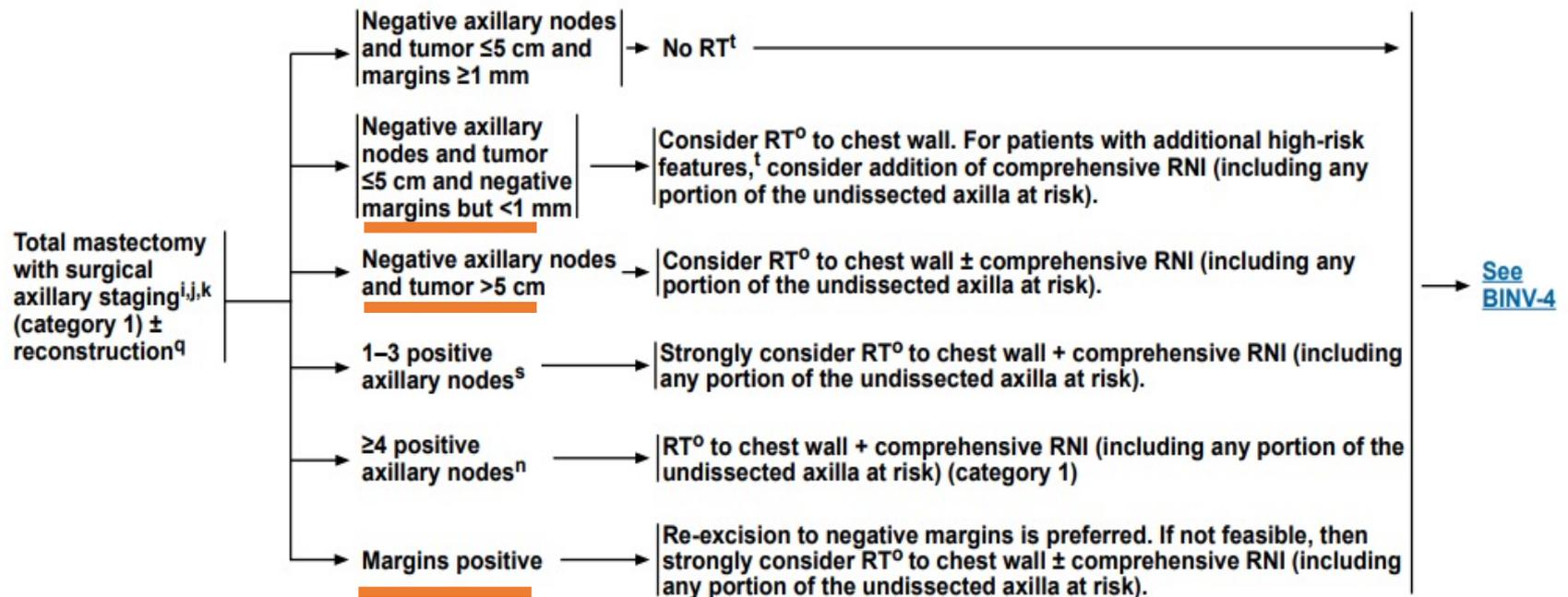
### RT AFTER COMPLETION OF BCS AND AXILLARY STAGING





**LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:<sup>a,f</sup>**  
**MASTECTOMY FOLLOWED BY RT**

**RT AFTER COMPLETION OF MASTECTOMY AND AXILLARY STAGING**



# Whole Breast Radiation

- Target definition is the breast tissue at risk
- RT dosing:
  - The whole breast should receive: a hypofractionated dose of 40–42.5 Gy in 15–16 fractions or in some cases 45–50.4 Gy in 25–28 fractions may be considered.
- Typical boost doses are 10–16 Gy in 4–8 fractions.
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy
- Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions may be considered for selected pts over 50 yrs following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended

## Chest Wall Radiation

- Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx; in 25-28 fractions patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx.
- Chest wall scar boost may be delivered with or without bolus using electrons or photons.

# Hypofractionated Radiotherapy in Breast Cancer

**START -> FAST -> FAST FORWARD**

# Whole breast radiotherapy after breast-conserving surgery

Whole breast RT:  
50 Gy in 25 fx

Hypofractionation: 40-  
42.5 Gy in 15-16 fx

Ultra-hypofractionation:  
26-28.5 Gy in 5 fx

1980s

2020

Milan, Gustave-  
Roussy, NSABP B-06,  
NCI, EORTC 10801,  
Danish trials

START A&B  
OCOG

FAST  
FAST-Forward

## START A

- 41.6Gy in 13Fr
- 39Gy in 13Fr
- 50Gy in 25Fr

## START B

- 40Gy in 15Fr
- 50Gy in 25Fr

Overall there was no significant difference in **loco-regional relapse** at 10 years:  
approximately 5-8% (for pT1-3 N0-N1)

Moderate or marked breast induration, telangiectasia, breast oedema were significantly  
less in 39Gy or 40Gy compared to 50Gy

## CANADIAN

- 42.5Gy in 16Fr
- 50Gy in 25Fr

## CHINESE

- 43.5Gy in 15Fr
- 50Gy in 25Fr

## DBCG

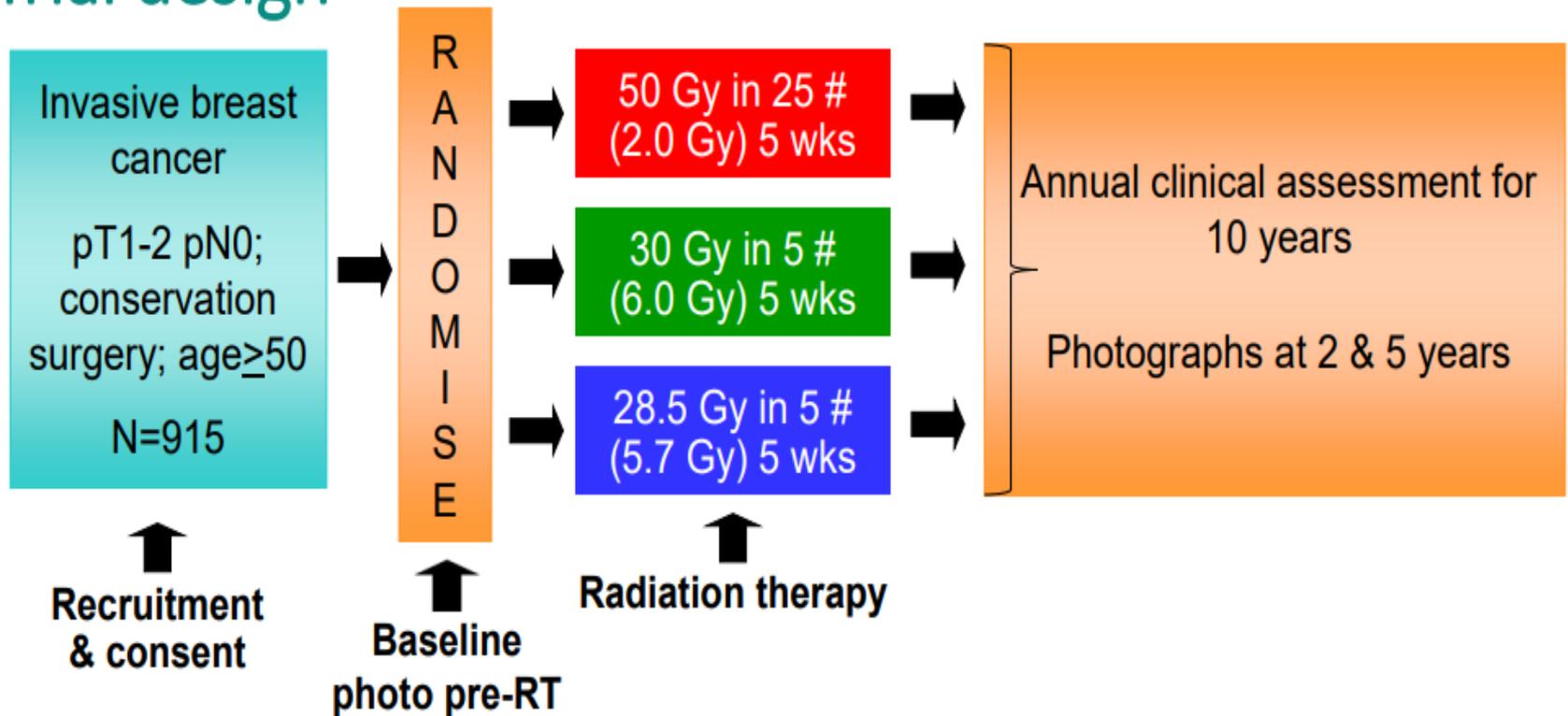
- 40Gy in 15Fr
- 50Gy in 25Fr

Randomised Phase 3 trials done in Canada, UK and subsequently in China and Denmark have confirmed the safety and efficacy of 15 fraction or 16 fraction schedules using 2.7Gy

Four of these trials published 10-year follow up data on a total 7000 patients, and 3-week schedules have replaced traditional regimens in many countries over the past decade.

**FAST Phase III RCT of Radiation Therapy  
Hypofractionation for Treatment of Early Breast Cancer:  
10-Year Results**

# Trial design



## Primary endpoint:

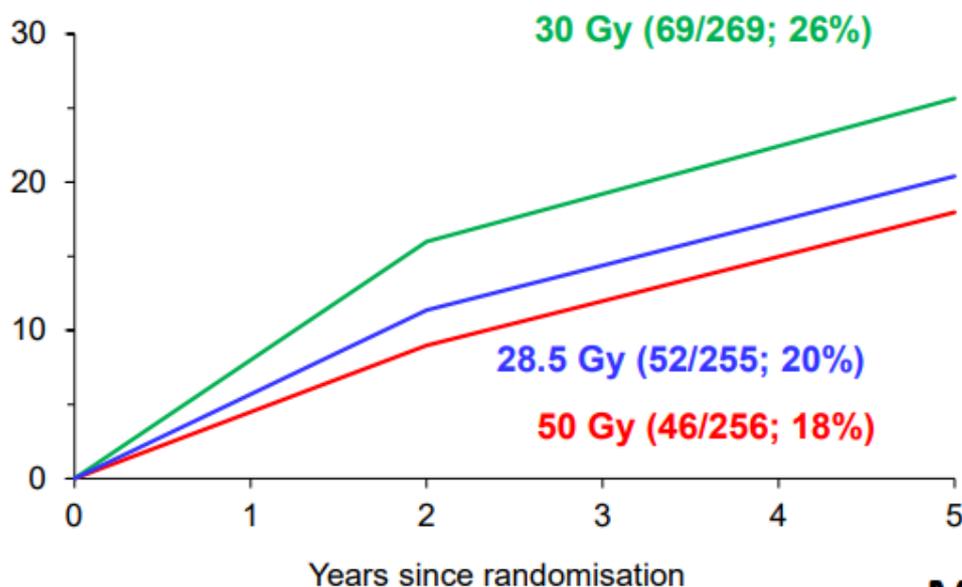
2-year change in photographic breast appearance

## Secondary endpoints:

5-year change in photographic breast appearance  
clinical assessments of late adverse events  
ipsilateral local tumour control

# Photographic assessment of overall change in breast appearance by 5 years

% with mild / severe change in breast appearance



**Difference (95%CI)**

**30Gy vs 50Gy**  
+7.4% (0.3, 16.7)  
p=0.03

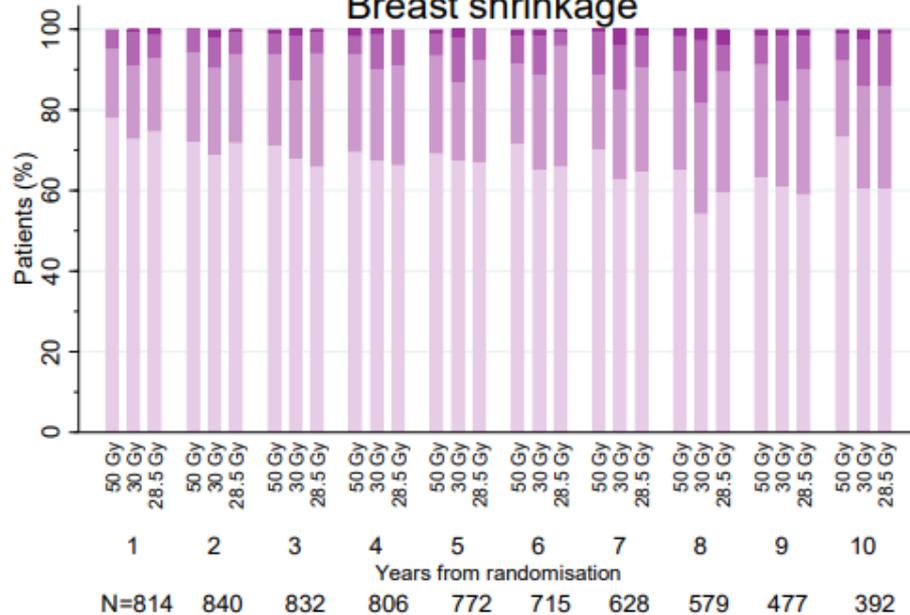
**28.5Gy vs 50Gy**  
+2.4% (-3.8, 10.8)  
p=0.47

**Marked changes: 2%, 4%, 2%**

# Clinical assessments of late AE in breast

None Mild Moderate Marked

Breast shrinkage

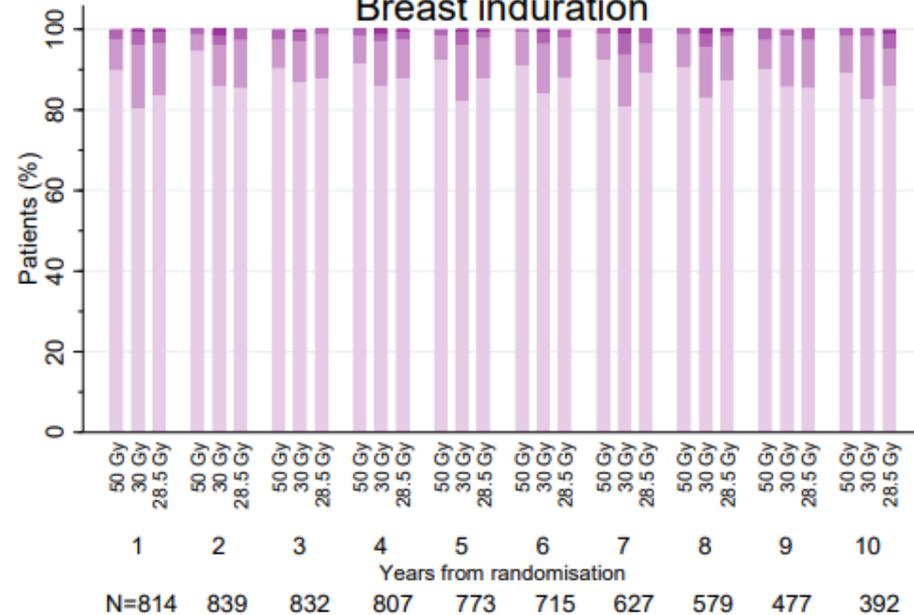


OR for moderate/marked shrinkage (95%CI)

30Gy vs 50Gy 1.88 (1.32, 2.67), p<0.001

28.5Gy vs 50Gy 1.11 (0.76, 1.64), p=0.59

Breast induration



OR for moderate/marked induration (95%CI)

2.39 (1.31, 4.35), p=0.004

1.67 (0.89, 3.16), p=0.11

## Relapse and survival at median 10 years' follow-up

	<b>50Gy/25# N=302</b>	<b>30Gy/5# N=308</b>	<b>28.5Gy/5# N=305</b>	<b>Total N=915</b>
<b>Local relapse</b>	3	4	4	11
<b>Regional relapse</b>	2	0	3	5
<b>Distant relapse</b>	17	15	15	47
<b>Death (breast cancer)</b>	30 (7)	33 (8)	33 (10)	96 (25)

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)

## Conclusions

- Severe changes to normal breast tissue were rare
- Late adverse events (AEs) after 28.5Gy/5# over 5 weeks similar to 50Gy/25#
- Little change in prevalence of AEs between 5 & 10 years
- Local tumour relapse rate extremely low in all schedules
- Once-weekly 5# schedule may be considered when daily visit for 3 or 5 weeks not acceptable
- UK FAST-Forward trial is testing 5# delivered in 1 week

**Hypofractionated Breast Radiotherapy for 1 week  
versus 3 weeks (FAST- Forward): A Multicentre, Non  
inferiority Randomised, Phase 3 Trial**

- Done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK.
- Patients aged at least 18 years with invasive carcinoma of the breast (pT1-3, pN0-1, M0) after breast conservation surgery or mastectomy.
- Whole breast or chestwall treatment, randomly allocated to :
  - ✓ 40Gy in 15 fractions over 3 weeks (2.67 Gy per fraction)
  - ✓ 27Gy in 5 fractions over 1 week (5.4Gy per fraction)
  - ✓ 26Gy in 5 fractions over 1 week (5.2Gy per fraction)

# FAST FORWARD

1368 patients treated in 26Gy in 5Fr arm

Very low LR at 5 years <2 % (non inferior)

Moderate or marked normal tissue effects in 121 of 1020(11.9%)

98 out of 986 patient in 40Gy arm (9.9%)

# Results

- Patient and photographic assessments showed higher normal tissue effect risk for 27Gy versus 40Gy but not for 26Gy versus 40Gy.
- Very low rate of cardiac events, rib fracture and symptomatic lung fibrosis.

# Results

**Table A5: Change in photographic breast appearance at 2 and 5 years (breast conservation surgery patients) by fractionation schedule: results of longitudinal analysis for 1309 patients with photographic assessments at 2 and/or 5 years**

	2 years				5 years				OR for mild / marked change vs 40Gy (95%CI)	Comparison with 40 Gy; p-value <sup>1</sup>	Comparison between 27 Gy & 26 Gy; p-value <sup>1</sup>
	N	None (%)	Mild (%)	Marked (%)	N	None (%)	Mild (%)	Marked (%)			
<b>40 Gy / 15Fr</b>	411	376 (91.5)	33 (8.0)	2 (0.5)	283	249 (88.0)	33 (11.7)	1 (0.3)	1	-	-
<b>27 Gy / 5Fr</b>	429	362 (84.4)	48 (11.2)	19 (4.4)	308	225 (73.1)	70 (22.7)	13 (4.2)	2.29 (1.60, 3.27)	<0.0001	-
<b>26 Gy / 5Fr</b>	427	381 (89.2)	33 (7.7)	13 (3.0)	284	247 (87.0)	28 (9.9)	9 (3.2)	1.26 (0.85, 1.86)	0.24	0.0006

<sup>1</sup> p-value from Wald test; OR = odds ratio (estimated from GEE model including 2 and 5-year data); 95%CI=95% confidence interval

# Interpretation

- 26Gy in five fractions is non inferior to the standard of 40Gy in 15 fractions over 3 weeks for local tumor control, and is safe in terms of normal tissue effects upto 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.

Normal tissue effects - Statistically not significant.  
Concern through the eyes of a clinician:?

- More moderate or marked events / total visits

	Number of moderate or marked events/total number of assessments over follow-up
Any adverse event in the breast or chest wall*	..
40 Gy	651/6121 (10.6%)
27 Gy	1004/6303 (15.9%)
26 Gy	774/6327 (12.2%)

#### What is more?

- Breast distortion
- Breast shrinkage
- Breast induration
- Telangiectasia
- Breast/chest wall edema
- Breast chest wall discomfort
- **NOT STATISTICALLY SIGNIFICANT**

#### What is less?

- Acute RTOG Grade 3 toxicity
- 6/44 (13.6%) in 40Gy
- 3/52 (5.8%) in 26Gy

# Should we wait...before recommending as the new standard for all breast radiotherapy?

- Against :
  - Late side effects are not better compared to 40Gy
  - In Photographic substudy only 1736 patients (accrual needed was 2196)
  - 10 year follow up to see the trend of late effects.
  - More precise planning and volume based DVH is required and cardiac shielding for left side cases.
  - Data from Lymph nodal radiotherapy started in 2015 awaited.
  - Widespread adoption of 40Gy/15Fractions happened after multiple RCTs, >7000 patients data and 10 year follow ups.

## St. Gallen/Vienna 2023: Optimization of Treatment for Patients with Primary Breast Cancer - a Brief Summary of the Consensus Discussion

- The Panel re-endorsed moderate hypofractionation (15-16 fractions over 3 weeks) as the standard of care (64% Yes)
- while some even advocated for ultra-hypofractionation (11) (5 fractions in 1 week, 11%).

➤ The Panel again **could not agree on the age** from which radiotherapy after breast conservation could **be omitted**;

in an overall favorable clinical situation (13mm tumor size, ER and PgR highly positive, Grade1), 41% of panelists would still offer adjuvant RT regardless of age (if life expectancy is >15 years), whereas other panelists suggest to omit RT for patients older than 65 (24%), 70 (29%), or 75 (13%). 27% of panelists claimed the importance of the PRIME-II trial(12) is that RT does not alter survival and therefore can be omitted, but 64% believe the trial shows that RT lowers in- breast recurrence.

A series of questions was asked on **postmastectomy radiation** (T2 tumor):

- ❖ In ER+ tumors and 1 micrometastasis, 89% of panelists do not recommend postmastectomy radiation therapy.
- ❖ With increasing disease burden, this percentage goes down:
  - 72% for 1 positive node, and
  - 35% for 2 positive nodes (a situation in which a majority, 53%, of panelists would already recommend postmastectomy radiation therapy).
  - For 3 positive nodes, 94% endorsed postmastectomy radiation therapy.
- ❖ For triple-negative disease, the threshold was generally lower, e.g. 23% Yes for micrometastasis.

✓ در درمان بیمار مبتلا به سرطان پستان HER2 مثبت با رزیدو پس از شیمی درمانی نئوآجوانت TCHP بهترین اقدام تغییر داروی آنتی HER2 به TDM1 است.

✓ در بیمار متاستاتیک دوره درمان آنتی HER2 تا زمان پیشرفت بیماری ادامه دارد. (در غیاب عارضه محدود کننده)

✓ در خصوص طول مدت اندوکسرین تراپی در بیمار مبتلا به سرطان پستان هورمون رسپتور مثبت stage 2 بسته به سایر ریسک فاکتورها و تحمل بیمار بین 5 تا 10 سال تصمیم گیری می شود.

✓ نتایج تریال keynote 522 منجر به اضافه شدن ایمونوتراپی به شیمی درمانی نئوآجوانت در بیماران تریپل نگاتیو شد.

✓ پمبرولیزوماب در دسته داروهای ایمونوترایی آنتی PDL1

✓ تراستوزوماب از دسته داروهای آنتی HER2

✓ رادیوترایی اجوانت بدنبال حفظ پستان منجر به کاهش ریسک عود لوکورژیونال (LRR) افزایش بقای اختصاصی بیماری (DSS) و بدرجاتی افزایش بقای کلی (OS) می شود.

✓ رادیوترایی کل پستان معمولا در 15، 16، یا 25 فراکشن انجام می شود.

✓ DCIS بدنبال توتال ماستکتومی با مارژین کافی اندیکاسیون رادیوترایی اجوانت ندارد.

✓ درگیری لنف نود با میکرومتاستاز اندیکاسیون قطعی رادیوترایی لنف نود نیست.

✓ همچنان درمان استاندارد در موارد عود سرطان پستان با سابقه جراحی حفظ پستان و رادیوترایی قبلی، توتال ماستکتومی است.



THANK YOU