Hypofractionation in Breast Cancer

Dr Grace Kusumawidjaja, FRCR (Clinical Oncology)
Radiation Oncologist, Senior Consultant
Mount Elizabeth Hospitals

Introduction

Globally:

- Breast ca caused 670,000 deaths (2022)
- #1 female cancer in 157 out of 185 countries (2022)

In Bangladesh:

- #1 of female cancer, #4 of all new cancer cases (2022)
- 18% (n= 12,989) among female new cancer cases (2022)
- #6 cause of cancer death (2022)

Source:
- https://www.who.int/news-room/fact-sheets/detail/breast-cancer#:~:text=In%202022%2C%20there%20were%202.3%20million%20women%20diagnosed,the%20breast%20cancer%20burden%20according%20to%20human%20development
- chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://gco.iarc.who.int/media/globocan/factsheets/populations/50-bangladesh-fact-sheet.pdf

Role of RT in breast ca and DCIS

- **Decrease risk of local relapse and improve survival in breast ca**
  - After lumpectomy[1]:
    - 10-year risk reduction of recurrence: ~15%
    - 15-year risk reduction of breast ca death: ~4%
  - After mastectomy[2] (when large tumor, axillary LN+):
    - 10-year risk reduction of recurrence: ~10-20%
    - 10-year risk reduction of breast ca death: 8%

- **Reduce ipsilateral breast relapse in DCIS:**
  - 10-year risk reduction by 15.2%

- **In palliative cases:** to alleviate patients' symptoms e.g. bleeding, pain, excessive discharge, local control

[1]EBCTCG MA, Lancet 2011.
[2]EBCTCG MA, Lancet 2014.
[3]EBCTCG, JNCIM 2010

At the very beginning … (2002)

Mount Elizabeth

TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

BERNARD FISHER, M.D., STEWART ANDERSON, PH.D., JOHN BRYANT, PH.D., RICHARD G. MARGOLESE, M.D., MELVIN DEUTSCH, M.D., EDWIN R. FISHER, M.D., JONG-HYEON JEONG, PH.D., AND NORMAN WOLMARK, M.D.

NSABP B6. NEJM 2002.

- Background: RCT, if BCS + RT = Mastectomy
- Methods:
  - n=1851, BCS alone vs BCS+RT vs mastectomy
  - **RT = 50 Gy in 25# over 5 weeks**
- Results:
  - cumulative incidence of recurrent ipsilateral breast recurrence = 39.2% vs 14.3% (BCS vs BCS+RT)
  - HR for death = 0.97 (p=0.74) BCS+RT vs mastectomy
- Conclusions: BCS+RT is appropriate treatment for breast ca

5TH BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

At the START (A B) … (2013)

Mount Elizabeth

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials *Lancet Oncol 2008; 9: 331–41*

- 1999 – 2002, 35 centers
- A: n=2236, 50Gy/25# vs 41.6Gy/13# vs 39Gy/13#
- B: n=2215, 50Gy/25# vs 40Gy/15#

- A: medianFU = 9.3y
- A: 10y-localregional relapse= [41.6Gy] 6.3% HR=0.91 p=0.65, [39Gy] 8.8% HR=1.18 p=0.41
- A: moderate/marked breast induration, teleangiectasia, breast edema – significantly less common in 39Gy vs 50Gy, but no significant difference between 41.6Gy vs 50Gy

5BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

At the START (A B) … (2013)

Mount Elizabeth

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Lancet Oncol 2008; 9: 331–41

- 1999 – 2002, 35 centers
- A: n=2236, 50Gy/25# vs 41.6Gy/13# vs 39Gy/13#
- B: n=2215, 50Gy/25# vs 40Gy/15#

- B: medianFU = 9.9y
- B: 10y-localregional relapse= [40Gy] 4.3% vs 5.5% [50Gy] HR=0.77 p=0.21
- B: breast shrinkage, teleangiectasia, breast edema were significantly less common in 40Gy

- Long term follow-up confirms that appropriately dosed hypofractionated RT is safe and effective. The results support the continued use of **40Gy in 15#.**

5BBCC

OCOG … NEJM 2010

Mount Elizabeth

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

- 1993 – 1996, 10 Canadian cancer centers
- medianFU = 12y
- n=1234, 50Gy/25# (n=612) vs 42.5Gy/16# (n=622)

- At 10y, local recurrence = 6.7% vs 6.2%
- At 10y, good or excellent outcome = 71.3% vs 69.8%

- 10y after treatment, accelerated hypofractionated whole breast irradiation [**42.5Gy/16#**] was not inferior to standard radiation treatment in women who had undergone BCS with clear margins and negative axillary LN

5TH BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

FAST-Forward ... to Lancet 2020

Mount Elizabeth

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

- 2011 – 2014, 97 centers
- 40Gy/15# (n=1361) vs 27Gy/5# (n=1367) vs 26Gy/5# (n=1368)
- Primary endpoint: ipsilateral breast tumor relapse
- Secondary endpoints: late AE, other survival outcomes (LRR, distant relapse, DFS, OS)
- Include pT1-3N0-1M0, BCS or mastectomy, SLNB or ALND
- Nodal RT was not allowed
- Concurrent endocrine tx and/or trastuzumab, but not concurrent chemotherapy
- Sequential boost: 16Gy/8# or 10Gy/5#

5TH BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

FAST-Forward ... to Lancet 2020

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
Local tumour control event (primary endpoint)*	31 (2·3%)	27 (2·0%)	21 (1·5%)
Local relapse	23 (1·7%)	22 (1·6%)	17 (1·2%)
Ipsilateral breast, new primary	6 (0·4%)	3 (0·2%)	4 (0·3%)
Cannot differentiate	2 (0·1%)	2 (0·1%)	0
Regional relapse	13 (1·0%)	11 (0·8%)	10 (0·7%)
Distant relapse	59 (4·3%)	69 (5·0%)	76 (5·5%)
Contralateral breast, second primary	23 (1·7%)	20 (1·5%)	23 (1·7%)
Invasive	18 (1·3%)	17 (1·2%)	20 (1·5%)
Ductal carcinoma in situ	5 (0·4%)	3 (0·2%)	2 (0·1%)
Unknown	0	0	1 (0·1%)
Non-breast, second primary	42 (3·1%)	37 (2·7%)	44 (3·2%)
Death	92 (6·8%)	105 (7·7%)	90 (6·6%)
Breast cancer†	47 (3·5%)	51 (3·7%)	53 (3·9%)
Second cancer	12 (0·9%)	16 (1·2%)	10 (0·7%)
Cardiac	10 (0·7%)	9 (0·7%)	8 (0·6%)
Other cause	17 (1·7%)	27 (2·0%)	16 (1·2%)
Unknown	6 (1·2%)	2 (0·1%)	3 (0·2%)

Data are n (%). Patients reporting events of more than one type are included in each relevant row. *Includes angiosarcoma in ipsilateral breast (one in the 40 Gy group and two in the 26 Gy group) and six patients with ductal carcinoma in situ (three in the 40 Gy group, two in the 27 Gy group, and one in the 26 Gy group). †Includes 13 patients with distant relapse before death from other causes (four in the 40 Gy group, four in the 27 Gy group, and five in the 26 Gy group).

- medianFU = 71.5m (~5.9y)
- ipsilateral breast tumor relapse (n=79):

  [40Gy] 31
  - vs [27Gy] 27

    HR 0.86 (95%CI 0.51-1.44)
  - vs [26Gy] 21

    HR 0.67 (95%CI 0.38-1.16)
- Most common cause of non-breast second primary ca: colorectal ca
- Of 27 cardiac-related death, 15 had h/o cardiac disease or current/ex-smokers

FAST-Forward ...

Incidence of locoregional & distant relapse, DFS, OS were similar in all groups

(no statistically significant difference)

	Cumulative number of events	Estimated cumulative incidence by 5 years (95% CI)	Hazard ratio (95% CI); p value	Estimated absolute difference vs 40 Gy at 5 years (95% CI)
Ipsilateral breast tumour (local) relapse*				
40 Gy (n=1361)	31 (2·3%)	2·1% (1·4 to 3·1)	1 (ref)	..
27 Gy (n=1367)	27 (2·0%)	1·7% (1·2 to 2·6)	0·86 (0·51 to 1·44); 0·56	−0·3% (−1·0 to 0·9)
26 Gy (n=1368)	21 (1·5%)	1·4% (0·9 to 2·2)	0·67 (0·38 to 1·16); 0·15	−0·7% (−1·3 to 0·3)
Locoregional relapse†				
40 Gy (n=1361)	43 (3·2%)	2·8% (2·0 to 3·9)	1 (ref)	..
27 Gy (n=1367)	35 (2·6%)	2·3% (1·6 to 3·3)	0·80 (0·51 to 1·25); 0·33	−0·5% (−1·4 to 0·7)
26 Gy (n=1368)	29 (2·1%)	1·8% (1·2 to 2·7)	0·66 (0·41 to 1·06); 0·083	−0·9% (−1·6 to 0·2)
Distant relapse				
40 Gy (n=1361)	59 (4·3%)	3·8% (2·9 to 5·0)	1 (ref)	..
27 Gy (n=1367)	69 (5·0%)	4·7% (3·7 to 6·0)	1·16 (0·82 to 1·64); 0·41	0·6% (−0·7 to 2·3)
26 Gy (n=1368)	76 (5·6%)	5·1% (4·0 to 6·4)	1·27 (0·90 to 1·79); 0·17	1·0% (−0·4 to 2·9)
Any breast cancer-related event‡				
40 Gy (n=1361)	119 (8·7%)	7·8% (6·5 to 9·4)	1 (ref)	..
27 Gy (n=1367)	112 (8·2%)	7·2% (5·9 to 8·7)	0·93 (0·71 to 1·20); 0·56	−0·6% (−2·2 to 1·5)
26 Gy (n=1368)	114 (8·3%)	7·5% (6·2 to 9·0)	0·94 (0·73 to 1·22); 0·65	−0·4% (−2·1 to 1·6)
All-cause mortality				
40 Gy (n=1361)	92 (6·8%)	5·4% (4·3 to 6·8)	1 (ref)	..
27 Gy (n=1367)	105 (7·7%)	6·9% (5·7 to 8·4)	1·12 (0·85 to 1·48); 0·42	0·6% (−0·8 to 2·5)
26 Gy (n=1368)	90 (6·6%)	5·6% (4·5 to 7·0)	0·96 (0·72 to 1·28); 0·78	−0·2% (−1·5 to 1·5)

Hazard ratios less than 1 favour five-fraction schedules. p values were calculated by log-rank test (two-sided). *Includes three patients with angiosarcoma in ipsilateral breast (one in the 40 Gy group and two in the 26 Gy group). †Defined as ipsilateral breast tumour relapse or regional relapse (axilla, supraclavicular fossa, and internal mammary chain). ‡Includes local, regional, or distant relapse, breast cancer death, or contralateral breast cancer (disease-free survival).

Table 2: **Relapse and mortality by fractionation schedule: time-to-event analysis (n=4096)**

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..
Breast distortion†	..	..	..	..	0·99 (0·95–1·02); 0·38
40 Gy	232/5724 (4·0%)	1 (ref)	..	..	..
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028	..	..
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19	0·083	..
Breast shrinkage†	..	..	..	..	1·03 (1·00–1·06); 0·023
40 Gy	330/5728 (5·8%)	1 (ref)	..	..	..
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004	..	..
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71	0·0018	..
Breast induration (tumour bed)†	..	..	..	..	1·00 (0·96–1·04); 0·95
40 Gy	185/5713 (3·2%)	1 (ref)	..	..	..
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013	..	..
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23	0·047	..
Breast induration (outside tumour bed)†	..	..	..	..	0·96 (0·90–1·02); 0·17
40 Gy	45/5712 (0·8%)	1 (ref)	..	..	..
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001	..	..
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013	0·059	..
Telangiectasia	..	..	..	..	1·21 (1·14–1·29); <0·0001
40 Gy	63/6087 (1·0%)	1 (ref)	..	..	..
27 Gy	100/6272 (1·6%)	1·68 (1·07–2·65)	0·025	..	..
26 Gy	102/6300 (1·6%)	1·53 (0·96–2·43)	0·070	0·65	
Breast or chest wall oedema	..	..	..	..	0·73 (0·69–0·78); <0·0001
40 Gy	89/6097 (1·5%)	1 (ref)	..	..	..
27 Gy	217/6287 (3·4%)	2·18 (1·57–3·03)	<0·0001	..	..
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032	0·0097	..
Breast or chest wall discomfort	..	..	..	..	0·93 (0·89–0·97); 0·0003
40 Gy	234/6086 (3·8%)	1 (ref)	..	..	..
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44	..	..
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86	0·35	..

Higher normal tissue effect risk for 27Gy vs 40Gy,
but not for 26Gy vs 40Gy

FAST-Forward ... to Lancet 2020

- At 5y, moderate or marked clinician normal tissue effects in breast/CW:
  [40Gy] 9.9% vs [27Gy] 14.4% vs [26Gy] 11.9%
- Across all clinician assessments from 1-5y:
  - OR for 40Gy vs 27Gy = 1.55, $p<0.0001$
  - OR for 40Gy vs 26Gy = 1.12, $p=0.2$

- **<u>26Gy in 5# over 1 week</u>** is non-inferior to the standard of 40Gy in 15# over 3 weeks for local tumor control, and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local RT after primary surgery for early-stage breast cancer.

Another FAST way … (2020)

Mount Elizabeth

Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Journal of Clinical Oncology
Volume 38, Issue 28 3261

- 2004-2007, 18 centers
- ≥50yo, pT1-2 (<3cm) N0, BCS only
- Exclusion criteria: mastectomy, nodal RT, tumor bed boost, cytotoxic tx
- 50Gy/25# (n=302) vs 30Gy/5# weekly (n=308) vs 28.5Gy/5# weekly (n=305)
- Primary endpoint: change in photographic breast appearance at 2y & 5y
- Secondary endpoint: physician assessments of normal tissue effects and local tumor control

- medianFU = 9.9y
- 11 ipsilateral breast ca event (n=3 vs 4 vs 4)
- 96 deaths (n=30 vs 33 vs 33)

5TH BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

Another FAST way … (2020)

Mount Elizabeth

Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Journal of Clinical Oncology
Volume 38, Issue 28 3261

- At 5y:
  - 79.5% (489/615) had no change in photographic breast appearance
  - 17.7% (109/615) had mild change, 2.8% (17/615) had marked change
- Rates of mild/marked change in photographic breast appearance at 2 or 5y were statistically significantly higher for 30Gy (OR=1.64, p=0.019), than for 28Gy (OR=1.1 p=0.686) vs 50Gy.
- For any moderate/marked breast normal tissue effects (shrinkage, induration, teleangiectasia, edema):
  - vs 30Gy: OR=2.12 p<0.001
  - vs 28Gy: OR=1.22 p=0.248

- At 10y, no significant difference in normal tissue effects after **28.5Gy in 5# (weekly)**, but higher after 30Gy.

Partial breast irradiation (PBI)

Mount Elizabeth

Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial *Lancet* 2017; 390: 1048–60

- 2007-2018, 30 centers
- 40Gy/15# WBI (n=674) vs **40Gy/15# PBI** (n=669)
- Eligibility: ≥50 yo, IDC, unifocal, ≤3cm tumor, margins ≥2mm, pN0
- Exclusion: mastectomy, previous ca, neoadjuvant chemo, M1
- Primary endpoint: ipsilateral local relapse
- medianFU = 72.2m

- 5y local relapse cumulative incidence 1.1% vs 0.5%
- Statistically significant lower AEs: change in breast appearance (p=0.007), breast harder or firmer (p<0.0001)

- **PBI is non-inferior compared with standard WBI in terms of local relapse in eBC, and equivalent or fewer late AEs**

5TH BBCC BANGLADESH BREAST CANCER CONFERENCE 2025

APBI

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

- 2005-2013, single center
- Eligibility: >40yo, ≤2.5cm tumor
- Excluded: extensive ca, multiple foci, margins <5mm
- WBI 50Gy/25# (n=260) vs APBI **30Gy/5# EOD** (n=260)
- MedianFU = 10.7y

- 10y cumulative incidence of IBTR = 2.5% vs 3.7% (HR1.56 p=0.4)
- APBI has significantly less acute toxicity (p=0.0001) and late toxicity (p=0.0001) and improved cosmetic outcome as deemed by physician (p=0.0001) and patient (p=0.0001)

APBI

Preliminary Results of a Randomized Study on Postmenopausal Women With Early Stage Breast Cancer: Adjuvant Hypofractionated Whole Breast Irradiation Versus Accelerated Partial Breast Irradiation (HYPAB Trial) CBC 2020

- 2015-2018, single center
- Eligibility: postmenopausal, cN0, unifocal, T1-2
- WBI (VMAT) 40.5Gy/15# with SIB 48Gy to tumor bed vs APBI (VMAT) **30Gy/5# EOD**
- Endpoint: cosmetic outcome
- medianFU = 36m

- 5 local failures and 3 locoregional failures (p=NS between arms)
- WBI – increased incidence of overall (62% vs 14%, p<0.001) and G2 (18% vs 1%, p<0.001) acute skin toxicity
- APBI – lower incidence of overall late toxicity (18% vs 41% p=).001)

- Local recurrence rate is low and comparable between 2 arms. Acute skin toxicity and overall late toxicity are significantly reduced with APBI.

ESTRO consensus, Lancet oncology 2022

- **Whole breast irradiation:**
  - 40Gy/15# - should be offered regardless of age at diagnosis, pT, breast ca biology, surgical margins status, tumor bed boost, breast size, invasive ca or DCIS, oncoplastic BCS, use of systemic tx
  - 26Gy/5# - can be offered as standard of care, or within a RCT or prospective registration cohort
- **Chest wall irradiation:**
  - 40Gy/15# - for CW RT without breast recon, and regardless of time and type of breast recon
  - 26Gy/5# - for CW RT without recon (can be offered as standard of care or within a RCT or prospective registration cohort)
- **RNI:** 40Gy/15#
- **PBI** (for low-risk) using EBRT: 40Gy/15# or 26Gy/5#

NCCN guidelines v1.2025

- Whole breast RT:
  - 40-42Gy in 15-16# (in selected cases 45-50.4Gy/25-28# may be considered)
  - 28.5Gy/5# *weekly* (for selected pts according to eligibility criteria)

- PMRT (incl recon)
  - 45-50.4Gy/25-28# or 40-42Gy in 15-16#

- RNI ≈ PMRT /whole breast RT

- PBI using EBRT
  - 30Gy/5# QOD
  - 40Gy/15#

RCR recommendation (RT dose fractionation, 4th ed, Jan 2024)

- Adjuvant RT to non-nodal breast or chest wall without immediate reconstruction: 26 Gy in 5 fractions over 1 week
- PBI using EBRT: 26 Gy in 5 fractions over 1 week
- RNI: 40 Gy in 15 fractions over 3 weeks
- In patients with co-morbidities and frailty making daily RT difficult: to consider 28.5 Gy in 5 fractions over 5 weeks

Summary

- Moderate hypofractionation (40Gy/15#) is safe
- Ultra-hypofractionation (26Gy/5#) is also safe, for whole or partial breast or chest wall irradiation without RNI
- When RNI is required – use moderate hypofractionation
- Mastectomy with immediate breast reconstruction – use moderate hypofractionation
- Patients with autoimmune disease, collagen vascular disease, vitiligo – use moderate hypofractionation
- Adhere to guidelines and safe protocols to ensure optimal PTV coverage and to minimize treatment toxicities

Mount Elizabeth™

THANK YOU!

Dr Grace Kusumawidjaja

Radiation Oncologist, Senior Consultant

3 Mount Elizabeth
Singapore 228510
Mount Elizabeth Hospital
Radiation Oncology Centre

38 Irrawaddy Rd Singapore 329563
Mount Elizabeth Proton Therapy Centre

Radiation Oncology, Senior Consultant
Mount Elizabeth Hospitals

Contact us

Tel: +65 6731 2782

Scan here for Whatsapp

Learn more

Scan here for website