

Ultra-hypofractionated whole breast radiotherapy for breast cancer

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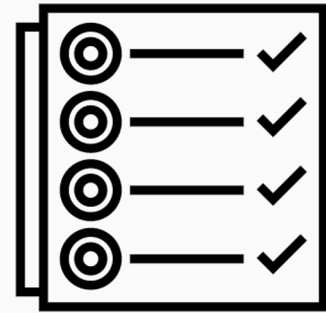
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Health

Brown Cancer Center

Objectives



To review key aspects of breast cancer ultra-hypofractionated radiotherapy including:

- Selection criteria
- Differences between ultra-hypofractionation and more protracted fractionation schemes
- Supporting data and literature
- Practical treatment planning considerations

Case

- 57-year-old female with abnormal screening mammogram
- ECOG: 0; KPS: 100
- PMHx: HTN, depression
- SurgHx: Hernia repair, tonsillectomy
- GYN: G1P1, menarche age 12, menopause age 50
- SocHx: No smoking, alcohol or illicit drug use
- Meds: HCTZ, sertraline
- FMHx: No family history of cancer
- Physical Exam: No palpable breast masses or adenopathy, skin abnormalities, or axillary/supraclavicular adenopathy. No bone tenderness

Case

- Screening MG: suspicious mass in the right breast, upper outer quadrant 3 cm from the nipple
- Diagnostic MG and U/S: confirm spiculated mass measuring 8 mm, no suspicious axillary adenopathy
- Core needle biopsy: invasive ductal carcinoma, ER positive, PR positive, and Her2/neu negative, grade 1
- Breast-conserving surgery and sentinel lymph node bx performed
- Path: IDC measuring 7mm, Grade 1, no associated DCIS, no LVI, 3 SLN negative, all margins negative by >5mm
- Pathologic stage: pT1b N0, IA

Adjuvant radiotherapy after breast-conserving surgery

- Omission in select patients (≥ 70 years of age, ER+, pN0, T1, low grade tumors receiving adjuvant endocrine tx) per PRIME-II, CALGB 9343, ongoing NRG BR007
- Whole breast radiation therapy +/-boost
- Partial breast radiation

Kunkler *et al.* Lancet Oncol 2015, Hughes *et al.* JCO 2013, White *et al.* NRG-BR007

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



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

START A&B
OCOQ

FAST
FAST-Forward

Benefits of ultra-hypofractionated radiotherapy

- More convenient for patients translating to improved compliance
- Radiobiologic advantage of ultra-hypofractionation in breast cancer due to low α/β ratio

Dragun *et al.* Cancer 2011. Whelan *et al.* NEJM 2010. Haviland *et al.* Lancet Oncology 2013

Indications for ultra-hypofractionated whole breast radiotherapy

- NCCN 2021: “For patients who require a more limited number of treatment visits for whole breast radiotherapy (WBRT) delivery, ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions, may be considered in ***selected patients*** age ≥ 50 following breast-conserving surgery with pTis/T1/T2/N0 tumors. However, late toxicity effects beyond 10 years are currently not defined”
- Royal College of Radiologists: “Offer 26 Gy in 5 fractions over one week for whole breast radiotherapy.” “Consider 28.5 Gy in 5 fractions over five weeks instead of 26 Gy in 5 fractions over one week for patients with significant co-morbidities and/or frailty that makes daily radiotherapy difficult”

NCCN Guidelines Version 8.2021 – September 13, 2021. Gradishar WJ, Moran MS, Abraham J, *et al.*
RCR consensus statements. May 2021.

COVID19 considerations

- 2020 COVID19 pandemic recommendation: “delivery of radiotherapy in five fraction only for all patients requiring radiation therapy with node negative tumors that do not require a boost is recommended”
- The use of 26 Gy in 5 fractions increased from 0.2% in 4/2019 to 60.6% in 4/2020 in the United Kingdom during the COVID19 pandemic

Coles *et al.* Clinical Oncology 2020. Spencer *et al.* Lancet Oncology 2021.

START A & B

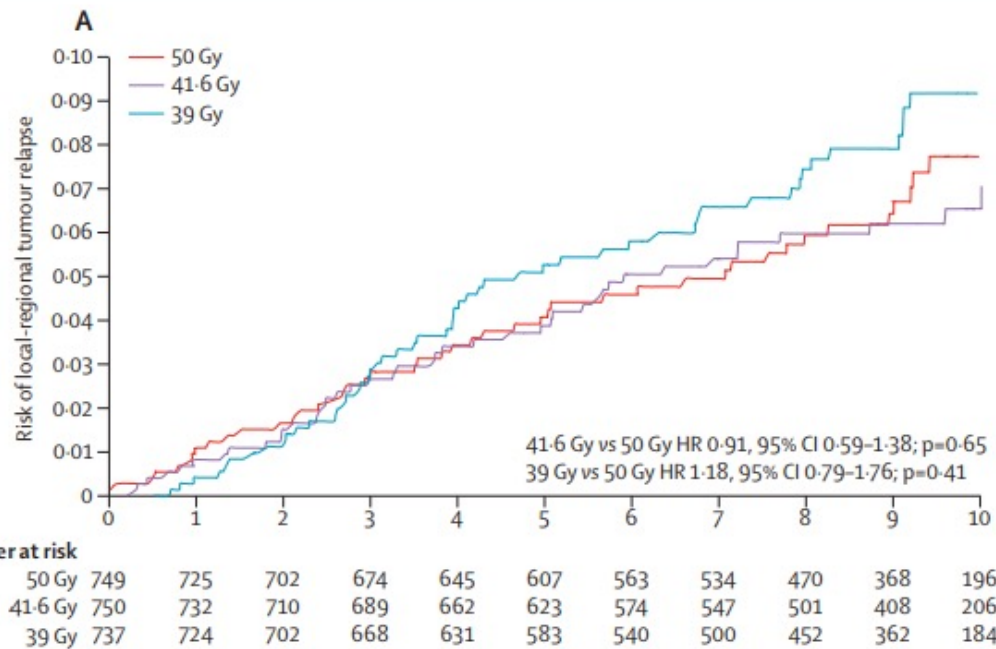
2236 pts, pT1-3a pN0-1 M0 s/p lumpectomy or mastectomy.
Chemotherapy and endocrine therapy allowed.

Whole breast radiation:

- START-A: 50 Gy in 25 fx in 5 wks vs 41.6 or **39 Gy in 13 fx** in 5 wks
- START-B: 50 Gy in 25 fx in 5 wks vs **40 Gy in 15 fx** in 3 wks

Conclusion: No difference in locoregional relapse or disease-free survival. Better toxicity outcomes with 39 Gy and 40 Gy, no difference in side effects between 41.6 and 50 Gy

Locoregional tumor relapse rate START-A



Locoregional tumor relapse rate START B

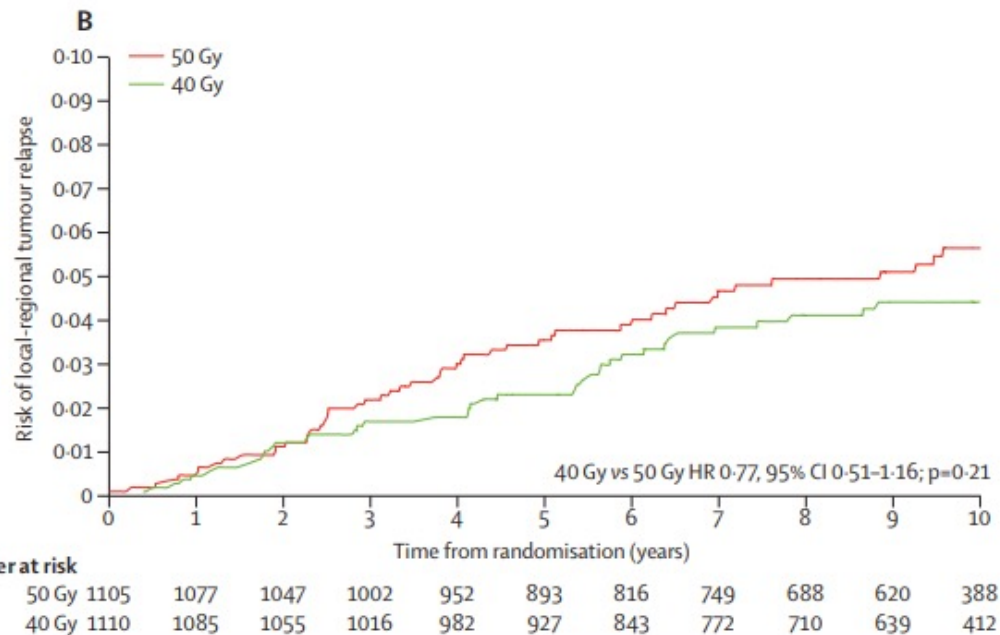


Figure 1: Cumulative risk of local-regional tumour relapse
In START-A (A) and START-B (B).

Whelan *et al* OCOG

1234 pts, pN0 early-stage breast cancer s/p breast-conserving surgery.

Whole breast radiation:

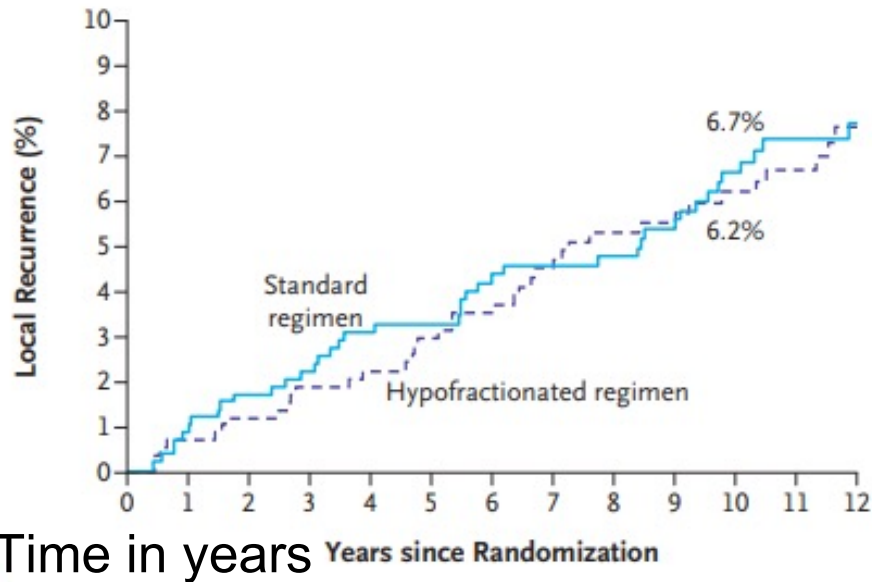
- 50 Gy in 25 fx over 5 wks
- **42.5 Gy in 16 fx** over 4 wks

Conclusion: No difference in oncologic or toxicity outcomes with hypofractionation

Whelan *et al*. NEJM 2010.

Local recurrence (%)

A

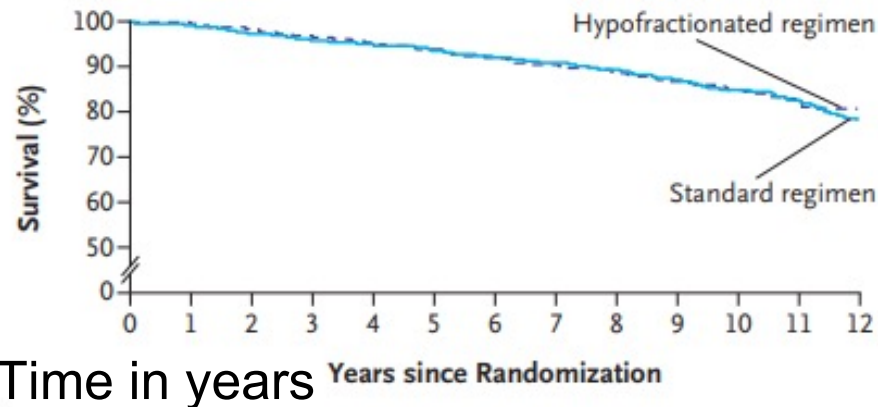


No. at Risk

Standard regimen	612	597	578	562	550	553	499	485	470	449	410	317	218
Hypofractionated regimen	622	609	592	569	548	524	500	472	447	430	406	330	214

Survival (%)

B



No. at Risk

Standard regimen	612	606	594	583	573	559	535	519	505	487	453	355	242
Hypofractionated regimen	622	617	605	592	576	562	539	517	495	482	455	369	241

UK FAST (CRUKE/04015)

915 pts \geq 50 yo, pT1-2 pN0, s/p breast-conserving surgery. No pts received chemo.

Whole breast radiation:

- 50 Gy in 25 fractions – control group
- **28 Gy** or 30 Gy *in 5 fractions* once a week over 5 weeks

Conclusion: No difference in oncologic outcomes or toxicity between arms although 30 Gy in 5 fx resulted in a higher rate of normal tissue effects up to 10 years (not 28 Gy in 5 fx)

TABLE 1. Change in Photographic Breast Appearance at 2 and 5 Years

Fractionation Schedule (Gy)	2 Years			5 Years			OR for Mild/Marked Change (95%CI)	Comparison With 50 Gy, P^a	Comparison Between 30 Gy and 28.5 Gy, P^a
	None No. (%)	Mild No. (%)	Marked No. (%)	None No. (%)	Mild No. (%)	Marked No. (%)			
50	217 (90.4)	20 (8.3)	3 (1.3)	163 (82.3)	31 (15.7)	4 (2.0)	1		
30	205 (82.7)	36 (14.5)	7 (2.8)	160 (75.5)	44 (20.8)	8 (3.8)	1.64 (1.08 to 2.49)	.019	
28.5	215 (88.1)	27 (11.1)	2 (0.8)	166 (81.0)	34 (16.6)	5 (2.4)	1.10 (0.70 to 1.71)	.686	.052

TABLE A6. Relapses, Second Primary Cancers, and Deaths, by Fractionation Schedule

Event	Fractionation Schedule			Total (N = 915)
	50 Gy (n = 302)	30 Gy (n = 308)	28.5 Gy (n = 305)	
Relapse				
Local (breast skin or parenchyma)	3 (1.0)	3 (1.0)	4 (1.3)	10 (1.1)
Regional (axilla or supraclavicular fossa)	2 (0.7)	0	3 (1.0)	5 (0.5)
Distant	17 (5.6)	15 (4.9)	15 (4.9)	47 (5.1)
Second primary cancer	23 (7.6)	21 ^a (6.8)	25 (8.2)	69 ^a (7.5)
Deaths	30 (9.9)	33 (10.7)	33 (10.8)	96 (10.5)
Breast cancer	7 (2.3)	8 (2.6)	10 (3.3)	25 (2.7)
Other cause	23 (7.6)	25 (8.1)	23 (7.5)	71 (7.8)
Second cancer	13	5	9	27
Cardiovascular	2	6	6	14
Pulmonary	2	8	2	12
Other	6	6	6	18

FAST-FORWARD

4096 pts, pT1-3 pN0-1, s/p breast-conservation surgery or mastectomy. Chemo allowed.

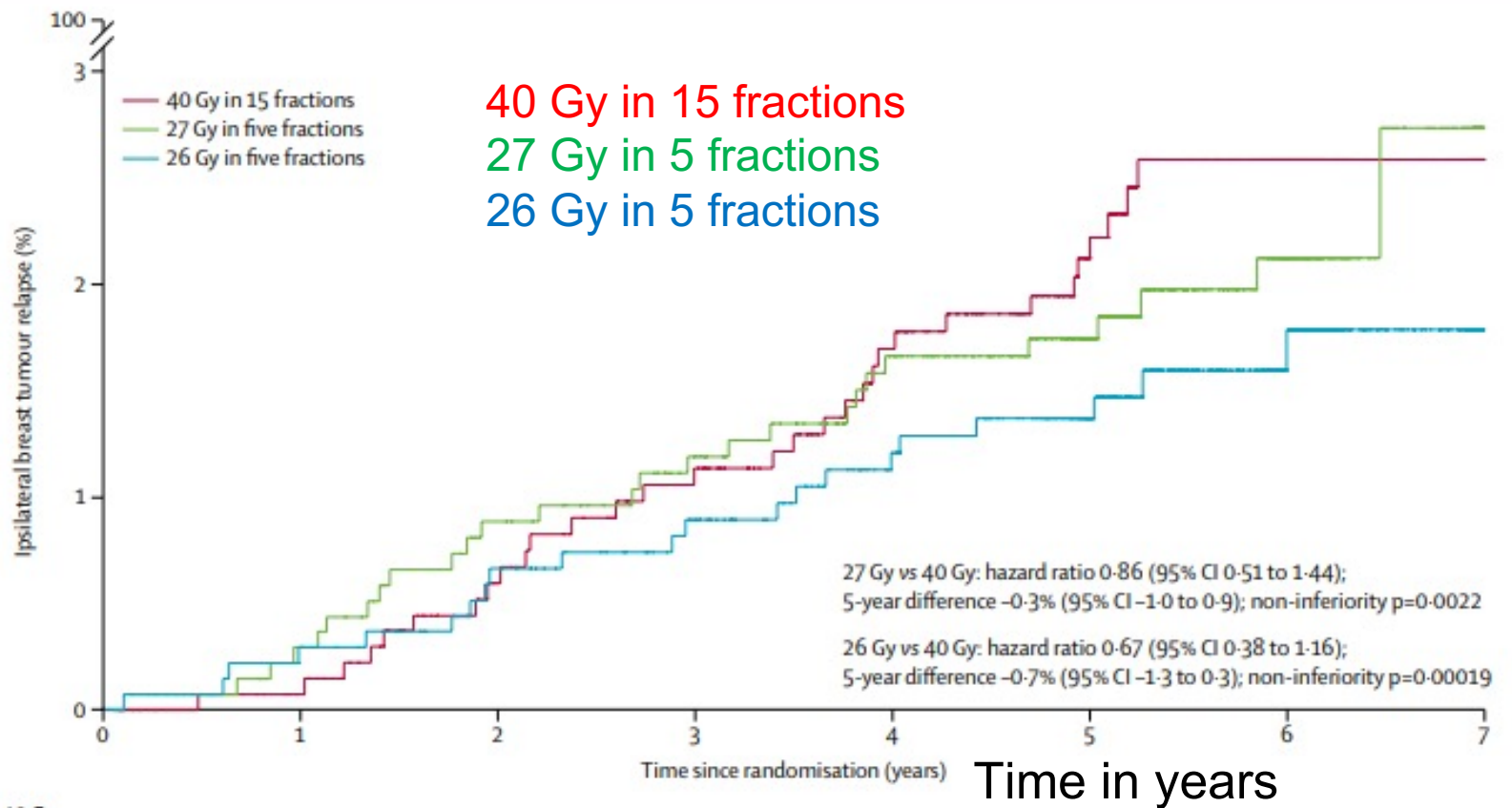
Whole breast radiation (WBI):

- 40 Gy in 15 fractions
- 27 Gy in 5 fractions in one week
- **26 Gy in 5 fractions in one week**

Conclusion: No difference in oncologic outcomes up to 5 years

Brunt *et al.* Lancet 2020.

Ipsilateral Breast Tumor Relapse



	0	1	2	3	4	5	6	7
40 Gy								
Number at risk	1361	1347	1307	1281	1230	1045	486	91
Censored	0	13	46	65	109	289	844	1239
Events	0	1	8	15	22	27	31	31
27 Gy								
Number at risk	1367	1352	1328	1303	1255	1066	508	90
Censored	0	11	27	48	90	278	833	1250
Events	0	4	12	16	22	23	26	27
26 Gy								
Number at risk	1368	1347	1325	1302	1257	1070	524	89
Censored	0	17	34	54	95	280	824	1258
Events	0	4	9	12	16	18	20	21

Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule

FAST-FORWARD

27 Gy led to significantly more adverse breast / chest wall events than 40 Gy

26 Gy was equivalent to 40 Gy in all measures of toxicity except for:

- 1) Breast induration: 0.8% vs 1.6% ($p = 0.013$ for 26 Gy)
- 2) Telangiectasias: 1% vs 1.6% ($p = 0.07$ for 26 Gy - NS)
- 3) Breast edema: 1.5% vs 2.4% ($p = 0.032$ for 26 Gy)

How clinically meaningful are these differences?

Brunt *et al.* Lancet 2020.

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Prospective single-arm trial

- 158 pts, stage 0-II, s/p breast conserving surgery
 - 10% node positive
 - 31% received CHT
 - 11% received tumor bed boost
- 1) **28.5 Gy in 5 fx** WBI – half of pts (2013-2015)
 - 2) 30 Gy in 5 fx WBI (2011-2013)

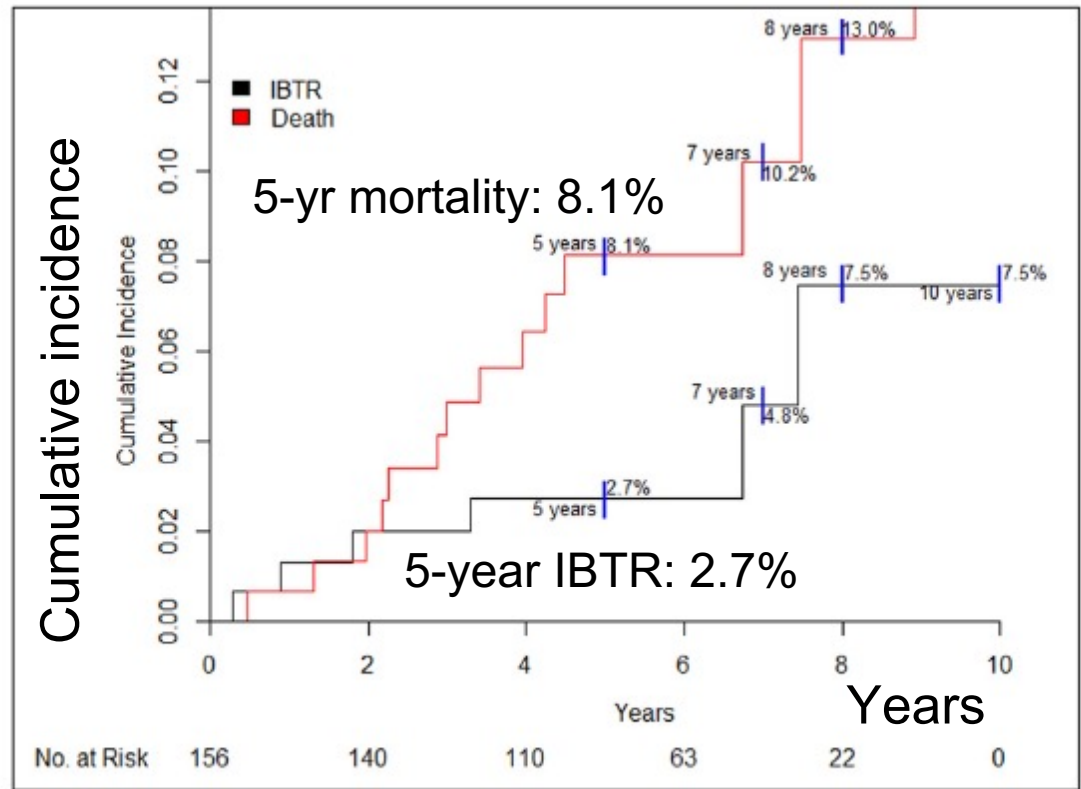


Fig. 1. Kaplan-Meier curve for ipsilateral breast tumor recurrence and mortality.

Conclusion: no difference in oncologic outcomes.

Patient-reported outcomes: mild-moderate cosmetic changes

Reshko *et al.* IJROBP 2022 and Eldredge-Hindy *et al.* IJROBP 2020

January 15, 2022

ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY



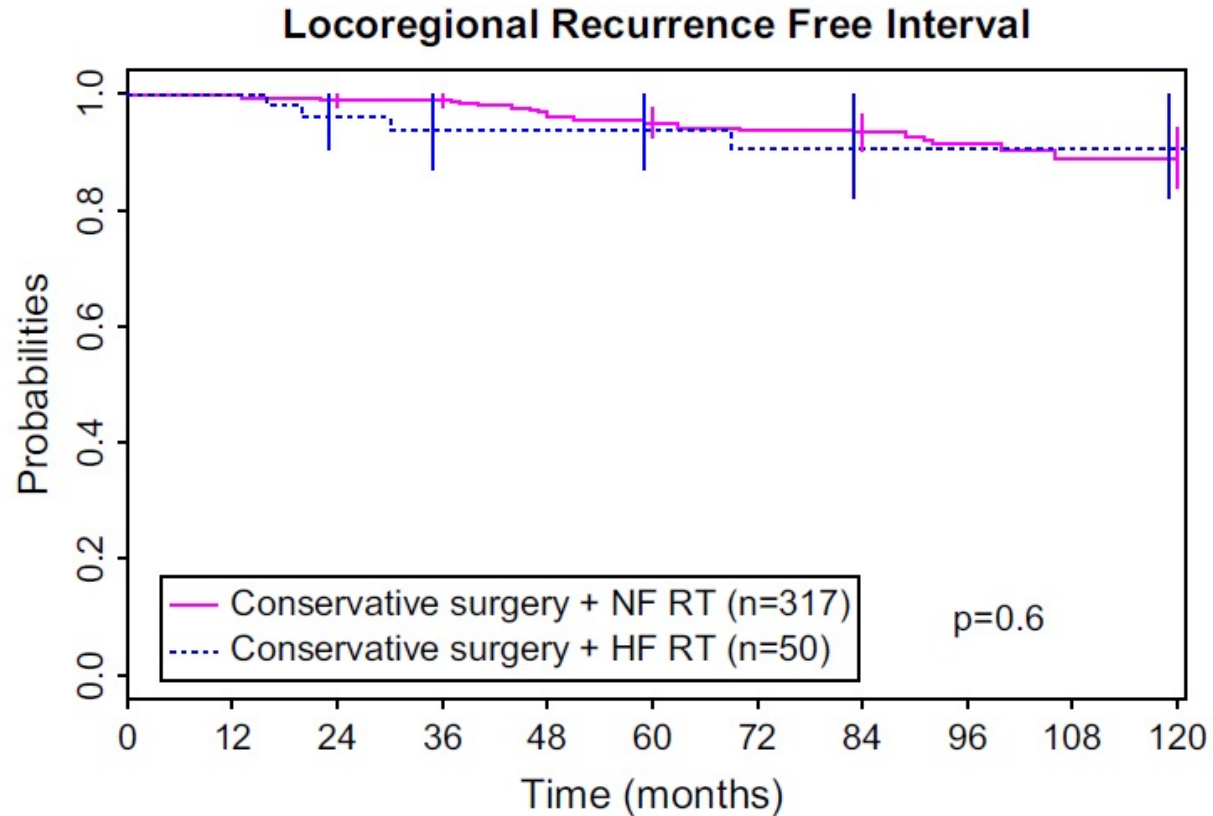
Institut Curie

Retrospective

- 367 pts s/p breast conserving surgery
- age ≥ 70
- 24% node positive
- 17% positive margins

- 1) 50 Gy in 25 fx WBI
- 2) **32.5 Gy in 5 fx WBI**

Conclusion: no difference in oncologic outcomes



n.risk	317	311	298	289	267	247	222	189	112	50	14
n.risk	50	49	46	43	39	36	27	16	7	3	1

Centre Antoine-Lacassagne

Retrospective.

- 150 pts
- 28.5% mastectomy, rest: BCS
- 34% node positive
- 3% received chemotherapy
- **32.5 Gy in 5 fx** WBI

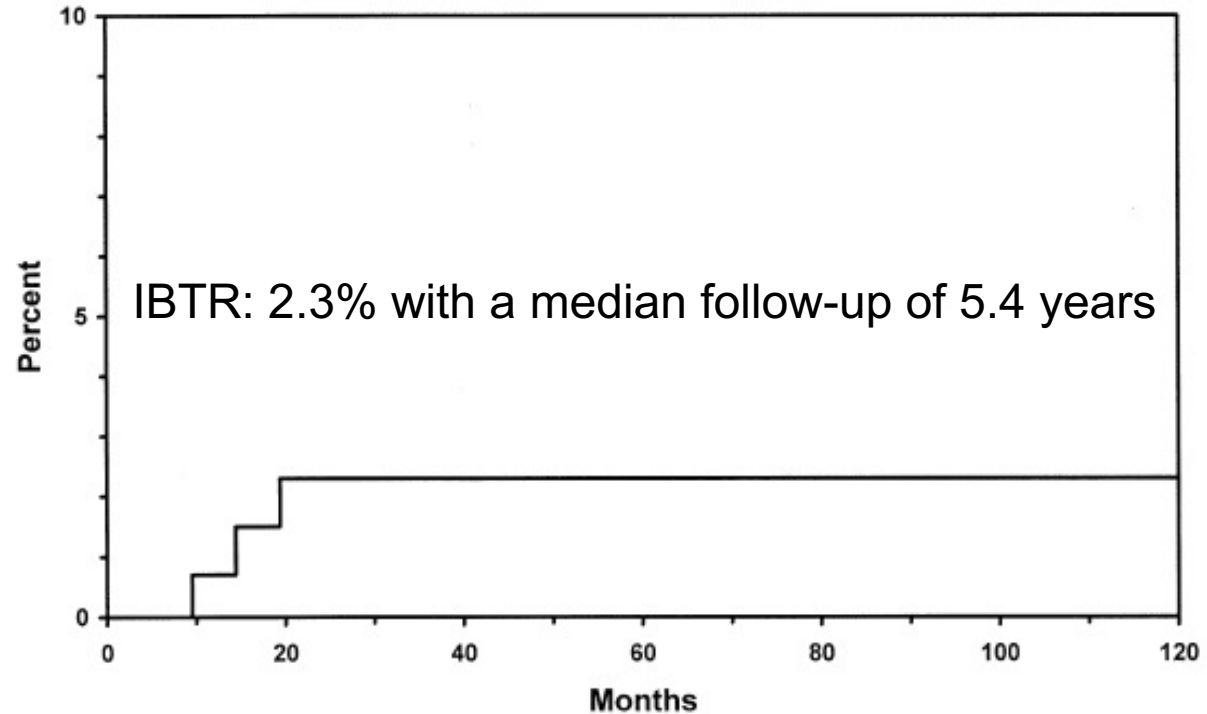


Fig. 5. Kaplan-Meier plot of local recurrence (LR); long-term estimate 2.3%.

Conclusion: mild early reactions and acceptable late toxicity, good long-term local control

Returning to our case

Would have qualified for START A&B, OCOG, FAST, and FAST-Forward trials. Considered suitable for APBI

WBI radiotherapy options: conventionally fractionated, hypofractionated, and ultra-hypofractionated radiotherapy

Patient was treated with ultra-hypofractionated WBI on an institutional protocol

Technical considerations

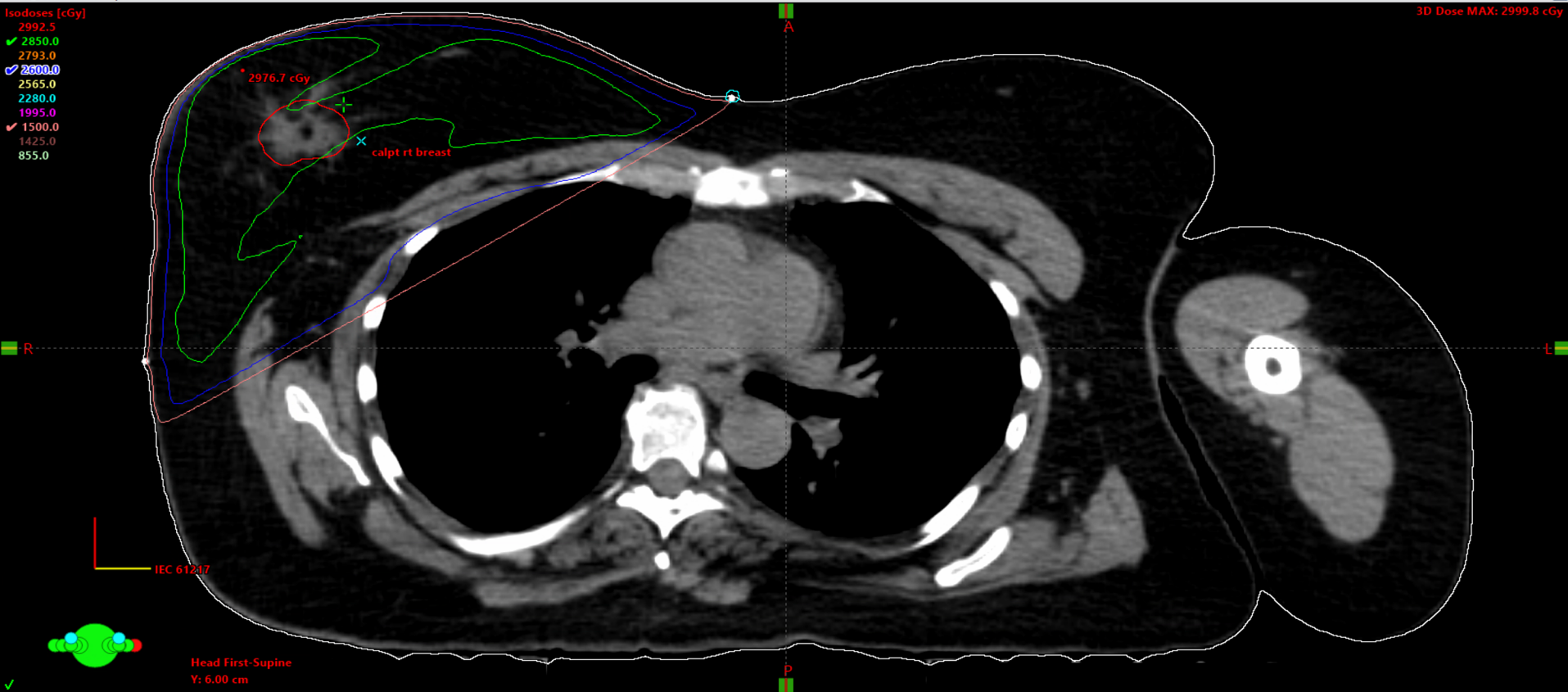
- Field-based 3D planning is utilized for whole breast radiotherapy – same as with hypofractionation
- FAST-Forward Planning Pack for the FAST-Forward Trial is an excellent resource
(https://d1ijoxngr27nfi.cloudfront.net/docs/default-source/default-document-library/fast-forward-planning-pack.pdf?sfvrsn=b5052169_0)
- Target localization: lumpectomy cavity clips

	CTV	PTV
Whole Breast (WB)	CTV _{WB} = Soft tissues of the whole breast, 5 mm below the skin surface	PTV _{WB} = CTV _{WB} + 10 mm margin
Chest Wall (CW)	CTV _{CW} = Skin flaps and soft tissues	PTV _{CW} = CTV _{CW} + 10 mm margin
Boost	CTV _{TB} = tumour bed	PTV _{TB} = CTV _{TB} + 10 mm margin

Brunt *et al.* Lancet 2020.

Isodoses [cGy]

2992.5
 ✓ 2850.0
 ✓ 2793.0
 ✓ 2600.0
 2565.0
 2280.0
 1995.0
 ✓ 1500.0
 1425.0
 855.0



- CT simulation was performed in a supine position, arms up in a breast board if tolerated (this pt could not elevate the left arm)
- Opposed tangential fields were used, field-in-field dose modulation with MLC-shaped segments, mixed energies (6 and 18 MV)
- Green color: prescription isodose line, red: lumpectomy bed, blue and brown: lower dose isodose lines

Contouring

Whole breast

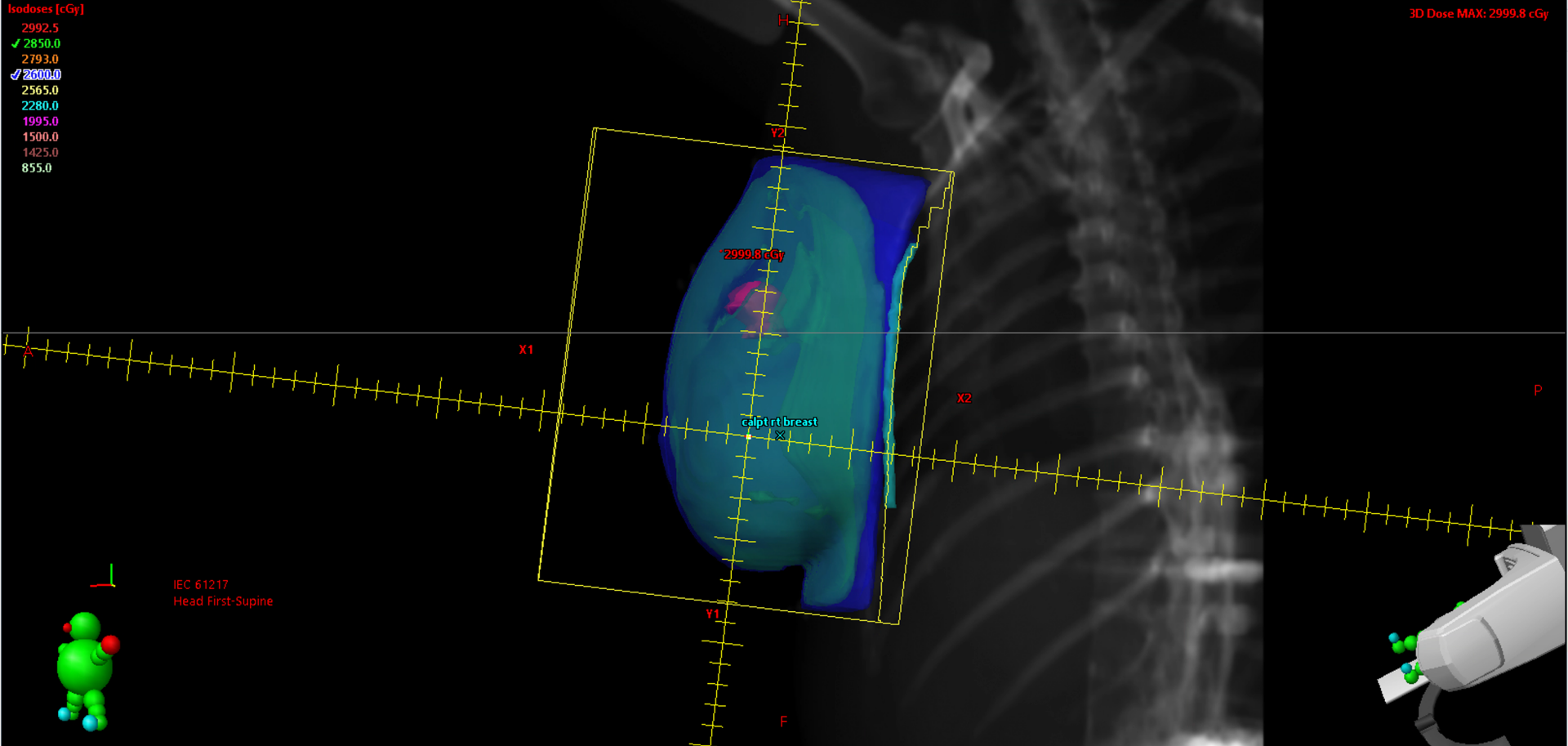
- Breast CTV: include glandular tissue; exclude chest wall
- Upper – bottom of clavicular head
- Inferior – 2cm below breast
- Lateral – 2cm beyond breast
- Medial – should not cross midline

Tumor bed

- Seroma and surgical clips

Heart

- Contouring atlas: Feng *et al.* IJROBP 2011



- Tangent field beam's eye view (BEV)
- Yellow rectangle: radiation field modulated by MLC's posteriorly
- Dark blue: 26 Gy dose, green: 28.5 Gy dose, red: lumpectomy bed

Dose constraints from FAST

Table 2: Upper and lower dose limits for whole breast PTV

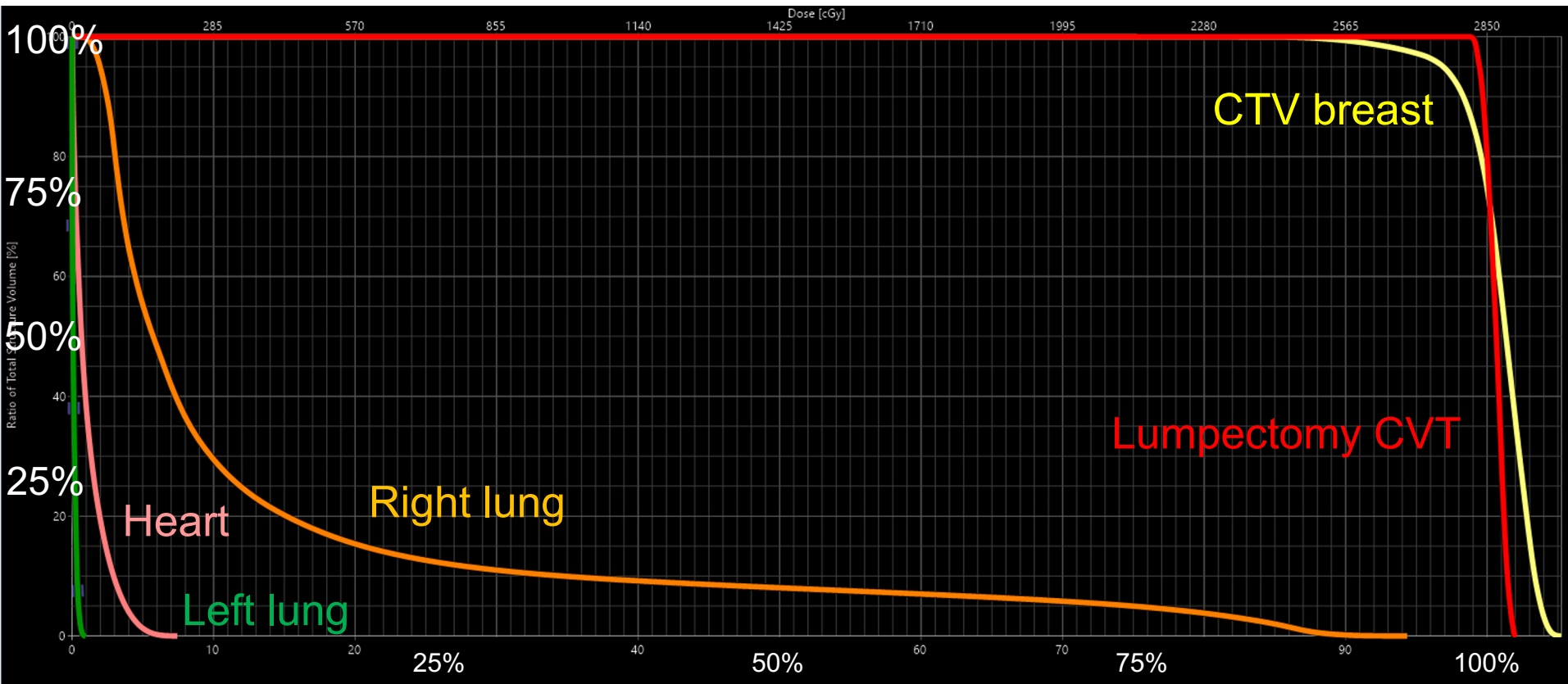
	Mandatory	Optimal
Lower limit	$V_{95\%} \geq 90\%$	$V_{95\%} \geq 95\%$
Upper limit	$V_{105\%} \leq 7\%$	$V_{105\%} \leq 5\%$
	$V_{107\%} \leq 2\%$	
	$D_{\max} \leq 110\%$	

Table 3: Dose constraints for organs at risk for whole breast and chest wall irradiation

	Mandatory	Optimal
Ipsilateral lung	$V_{30\%} \leq 17\%$	$V_{30\%} \leq 15\%$
Heart	$V_{25\%} \leq 5\%$	
	$V_{5\%} \leq 22\%$	

Planning Pack for the FAST-Forward Trial. Version 3. May 2013

DVH



Treatment planning

- This patient did not undergo a boost as her risk of local recurrence was deemed sufficiently low
- Lumpectomy bed boost to 10-16 Gy in 2-Gy fractions sequentially was done in 25.1% of patients in FAST-FORWARD but none of the patients in FAST received a boost
- Deep-inspiration breath hold scan (DIBH) may be obtained to reduce the heart dose in left-sided tumors
- Daily portal imaging is used for treatment verification

Post-treatment considerations

- Same as for conventionally-fractionated
- Follow-up: H&P 1-4/year x 5 years, then annually
- Mammography every 12 months
- Medical Oncology follow-up for endocrine therapy / chemotherapy
- Lifestyle considerations: active lifestyle, healthy diet, limited alcohol intake, and achieving and maintaining a BMI of 20-25
- Survivorship clinic

Additional considerations

Ongoing randomized trials comparing ultra-hypofractionation to hypofractionated WBI:

- NCT03788213 in India (26 Gy in 5 fx vs 40 Gy in 15 fx)
- NCT04434677 in Egypt (26 Gy in 5 fx vs 40.05 Gy in 15 fx)

Conclusions

- Ultra-hypofractionated WBI is a viable treatment modality for select early-stage breast cancers and is endorsed by NCCN, RMR, and COVID19 pandemic guidelines
- Ultra-hypofractionation offers equivalent oncologic and toxicity outcomes, superior patient convenience, improves radiotherapy compliance, and takes advantage of the low α/β ratio of breast cancer
- Lack of 10-year follow-up in FAST-FORWARD is a limitation of this technique

Beyond the scope of this ARROcase: accelerated partial breast irradiation, lumpectomy bed boost indications, dose and fractionation in the setting of ultra-hypofractionation, regional nodal irradiation for central/medial tumors or tumors > 2 cm with extensive LVI or young age, and how the Oncotype score factors into radiation therapy decision-making

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