RADIATION ONCOLOGY | 2025–2026

Hypofractionation, Ultrahypofractionation & DIBH in Breast Cancer

Current Standards & Future Recommendations

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RADIOBIOLOGICAL BASIS

Why breast cancer is ideally suited to hypofractionation

α/β Breast Cancer

~3.4 Gy

Fowler 2006 / Haviland 2013

α/β Late Normal Tissue

~3 Gy

Similar to tumor — rare in oncology

α/β Acute Skin

~8–10 Gy

Higher; large fx may worsen acutely

🔑 **Key Insight:** Low α/β ratio of breast tumour (~3.4 Gy) means larger fraction sizes are proportionally MORE lethal to tumour than to late normal tissues → hypofractionation is BIOLOGICALLY FAVOURED.

Schedule	Dose / Fx	Total Dose	BED_3 (Tumour)	EQD2 (Tumour)
Conventional 50 Gy/25 fx	2.0 Gy	50 Gy	83.3 Gy	50.0 Gy
START-B 40 Gy/15 fx	2.67 Gy	40 Gy	75.6 Gy	45.3 Gy
Canadian 42.5 Gy/16 fx	2.66 Gy	42.5 Gy	80.1 Gy	48.0 Gy
FAST-Forward 26 Gy/5 fx	**5.2 Gy**	**26 Gy**	**97.9 Gy**	**58.7 Gy**

HYPOFRACTIONATION

Landmark Randomised Controlled Trials

START-A

N = 2,236

Haviland et al. Lancet Oncol 2013

Arms:

→ 50 Gy/25 fx

→ 41.6 Gy/13 fx (3.2 Gy/fx)

→ 39 Gy/13 fx (3.0 Gy/fx)

Key Result:

41.6 Gy non-inferior for local control at 10 yr.
39 Gy marginally inferior.

3.2 Gy/fx = safe upper limit

START-B

N = 2,215

Haviland et al. Lancet Oncol 2013

Arms:

→ 50 Gy/25 fx

→ 40 Gy/15 fx (2.67 Gy/fx)

Key Result:

Non-inferior LC & OS at 10 yr. Fewer late effects (breast shrinkage, induration).

40 Gy/15 fx → Global standard

Canadian Trial

N = 1,234

Whelan et al. NEJM 2010

Arms:

→ 50 Gy/25 fx

→ 42.5 Gy/16 fx (2.66 Gy/fx)

Key Result:

10-yr LC 84.4% vs 83.6%. Similar cosmesis & OS.

42.5 Gy/16 fx widely used in N.America

HF-WBI: Meta-analysis Evidence & Clinical Guidelines

EBCTCG Meta-analysis 2021

Lancet 2021 | N = 8,135

✓ HF (15–16 fx) vs Conv (25 fx): no significant difference in 10-yr local recurrence

✓ Late adverse effects marginally LOWER with HF (breast induration, teleangiectasia)

✓ No subgroup interaction for tumour grade, age, or receptor status

✓ Boost dose: equivalent benefit maintained in HF arms

Current Guidelines (2023–2025)

ASTRO 2022

HF preferred for whole breast RT (strong) — for node-negative and node-positive early BC

ESMO 2023

HF standard for early BC; UHF (5 fx) evidence sufficient for recommendation in select patients

ESTRO 2022

40 Gy/15 fx or 42.5 Gy/16 fx as standard; FAST-F schedule for UHF

India IROG

HF endorsed; resource-constrained settings may consider 5-fx schedules (institutional protocols)

FAST Trial — The Proof of Concept

Trial:	FAST (UK)
Publication:	Brunt et al. JCO 2020 (10-yr data)
Population:	N = 915 | Age ≥50 | T1-2N0 | Post-BCS
Control Arm:	50 Gy / 25 fx (2.0 Gy/fx)
Experimental 1:	30 Gy / 5 fx (6.0 Gy/fx) — once weekly
Experimental 2:	28.5 Gy / 5 fx (5.7 Gy/fx) — once weekly

10-Year Results

Outcome	50 Gy/25	28.5 Gy/5	30 Gy/5
Local recurrence	1.1%	1.3%	2.0%
Moderate/Marked photo-dam.	9.5%	13.3%	27.8%
Breast induration	0%	0.9%	4.6%
Breast oedema	0.6%	2.5%	7.0%

✅ 28.5 Gy/5 fx: Non-inferior LC with acceptable late effects
⚠️ 30 Gy/5 fx: Higher photodamage — NOT recommended

FAST Conclusion: Once-weekly 5-fraction delivery is feasible and effective in select early breast cancer. 28.5 Gy/5 fx emerged as the safer dose. This trial set the stage for FAST-Forward.

FAST-FORWARD TRIAL

Murray Brunt et al. — Lancet 2020 (5-yr) & 2023 (update)

Study Design

- N = 4,096 patients
- Invasive BC, pT1-3N0-1
- Post-BCS (96%) or mastectomy
- 40 Gy/15 fx (standard)
- 27 Gy/5 fx (once daily)
- 26 Gy/5 fx (once daily)

Primary Endpoint: 5-year Local Tumour Relapse

Arm	5-yr LTR	Difference vs 15 fx	Verdict
40 Gy/15 fx	2.1%	—	Reference
27 Gy/5 fx	1.7%	–0.4% (–1.1 to 0.2)	Non-inferior ✅
26 Gy/5 fx	1.4%	–0.7% (–1.3 to 0.0)	Non-inferior ✅

Late Toxicity at 5 Years (any Mod/Marked)

Toxicity	40 Gy/15	26 Gy/5	27 Gy/5
Breast hardness	9.8%	9.9%	15.0%
Breast shrinkage	12.3%	15.1%	20.0%
Photodamage	2.0%	4.4%	6.0%
Skin oedema	3.0%	4.9%	7.0%

26 Gy / 5 fx

(5.2 Gy/fx, consecutive days)

Recommended dose: Non-inferior LC, lower toxicity than 27 Gy/5 fx. Equivalent to 15-fx HF. Treatment in 1 week. ASTRO & ESTRO endorsed.

FAST-Forward in Practice: Who, When & How

✅ Ideal Candidates

- ✓ pT1-2, N0 or N1 (up to 3 nodes) post-BCS
- ✓ Age ≥50 (HER2−, hormone receptor+ predominance)
- ✓ Small-moderate breast size (uniform dose distribution)
- ✓ No prior breast/chest RT
- ✓ Patient requesting shorter treatment course
- ✓ Resource-constrained / travelling patients
- ✓ Post-mastectomy: institutional protocol basis

⚠️ Use with Caution / Avoid

- ⚠ Large, pendulous breasts (dose inhomogeneity >±7%)
- ⚠ Bilateral simultaneous whole-breast RT
- ⚠ Active connective tissue/autoimmune disease
- ⚠ Pregnancy (relative CI)
- ⚠ N2-3 nodal disease (insufficient FAST-F data)
- ⚠ Inflammatory breast cancer
- ⚠ Brachytherapy/IORT boost planned

Boost with UHF: Current Evidence

FAST-Forward did NOT include a sequential or simultaneous integrated boost. Boost data are extrapolated from HF trials (e.g. IMPORT HIGH). Sequential boost (8–16 Gy in 4–8 fx) is commonly added, but routine use adds complexity. SIB approach (e.g. 26 Gy + 30 Gy/5 fx to tumour bed) is exploratory — investigate in trial setting. Decision should be multidisciplinary.

NODAL IRRADIATION & SIB: IMPORT HIGH Trial

IMPORT HIGH (Lancet 2023)

Coles et al. | N = 2,617

Post-BCS, lymph node+ or high-risk node–

Control: 40 Gy/15 fx WBI

+ 16 Gy/8 fx seq boost

Test 1: 36 Gy/15 fx (partial)

2.4 Gy/fx, reduced dose region

Test 2 (SIB): **40 + 48 Gy/15 fx**

SIB 3.2 Gy/fx to tumour bed

Key Results (5-yr)

Outcome	Control	SIB	p / HR
Local-regional relapse	3.6%	4.0%	NS
Dist-free survival	79.5%	78.8%	NS
Photodamage ≥Mod	14.5%	18.3%	0.03
Breast induration ≥Mod	9.9%	12.7%	0.05

SIB Conclusion: SIB non-inferior for control but mild excess late toxicity. Acceptable trade-off in high-risk patients — avoids extra RT visit for sequential boost.

SIB with 15 fx HF is now an evidence-based boost option

Regional Nodal HF: ASTRO 2022

Sufficient evidence to use HF (40 Gy/15 fx) for regional nodal RT including IMC. PRIMETIME trial (40 Gy/15 fx with nodal fields, ongoing) will provide confirmatory data. European practice (ESTRO) already endorses HF nodal RT based on current evidence.

Cardiac Rationale: Why Heart Dose Matters

Darby et al. NEJM 2013

N = 2,168 women | Swedish/Danish registry

7.4%	Increase in major coronary events per 1 Gy increase in mean heart dose (MHD)
Linear	No threshold — any increase in MHD raises risk proportionally
10–15 yr	Excess risk begins ~5 yr, highest at 10–15 yr post-RT
LCA	Left coronary artery (LCA/LAD) is primary OAR of concern in left-sided breast RT

DIBH Mechanism & Dosimetric Benefit

- ▶ Deep breath → diaphragm descends → lungs inflate → chest wall moves anteriorly
- ▶ Heart displaced posteriorly and inferiorly — away from tangential fields
- ▶ Mean heart dose reduction: 1.5–3.0 Gy (up to 50–70% reduction vs FB)
- ▶ Mean LAD dose reduction: 3–8 Gy (left-sided lesions)
- ▶ Ipsilateral lung V20: marginally improved with DIBH
- ▶ Right-sided: less benefit for cardiac dose; lung dose may still improve

Clinical Trigger: Use DIBH if estimated MHD >3–4 Gy (free breathing plan) in left-sided breast RT — threshold commonly used per ESTRO ACROP 2020 guidance. Some centres use <2 Gy as aspirational target.

DIBH: Clinical Evidence Base

DBCG IMN Study

Thorsen et al. Radiother Oncol 2016

Design: 10,416 pts, Danish registry; IMN irradiation impact on cardiac events

Finding: Cardiac death HR 1.27 (95% CI 0.88–1.84) with IMN-RT in left-sided disease

→ Reinforces need for cardiac dose reduction strategies

HYPOSIB (ABC Phase II)

Brunt et al. Lancet Oncol 2021

Design: Left-sided BC, DIBH with 26 Gy/5 fx UHF

Finding: MHD <2 Gy in 92% of patients. 11% with MHD >3 Gy without DIBH achieved compliance with DIBH.

→ DIBH compatible with FAST-Forward schedule — feasible in real-world practice

DIBH Meta-analysis

Bartlett et al. IJROBP 2013

Design: Meta-analysis: 12 studies, DIBH vs free breathing dosimetry

Finding: MHD reduction: 46% (3.1 Gy absolute reduction). LAD dose: 49% reduction.

→ Dosimetric benefit is consistent and clinically meaningful

ESTRO ACROP Guidance

Sautter-Bihl et al. Radiother Oncol 2020

Design: Expert consensus on heart-sparing in breast RT

Finding: Recommend DIBH for left-sided if MHD >4 Gy in FB plan. DIBH target: MHD <3 Gy, LAD max <30 Gy

→ Standardises DIBH indications across European practice

DIBH EXPERIENCE

Institutional Data — Left-Sided Breast RT

45
Total DIBH patients
(Aug 2019 – 2023)

35
Left-sided breast
cancer patients

13
Post-mastectomy
(MRM) patients

12
Treated with HF
(40 Gy/15 fx)

Dosimetric Results (RGSC Gating)

Mean cardiac dose (DIBH)
2.1 Gy SD 0.9

Average V20 left lung
16.3% SD 5.2

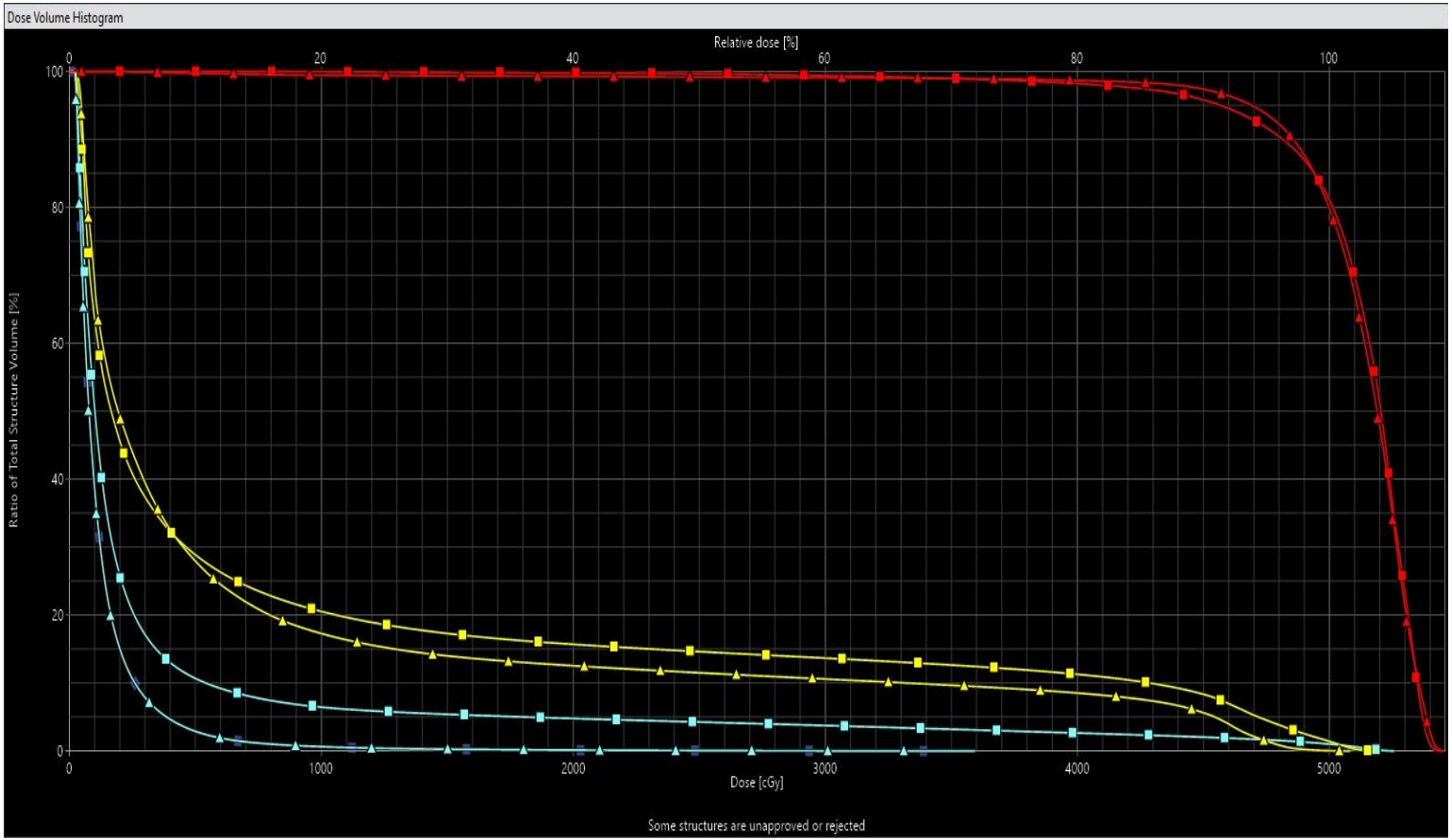
DIBH

	Lung V20Gy (%)	Lung V30Gy (%)	Lung V15Gy (%)	Lung V25Gy (%)	Lung Mean (Gy)	Heart Mean (Gy)
Average	16.3	14.1	17.8	15.2	9.3	2.1
SD	5.2	5.3	5.3	5.2	2.8	0.9

Conclusions:

DIBH reduces mean cardiac dose by ~41% and lung V20 by ~20% vs free breathing. **All patients with left-sided breast cancer are now offered DIBH routinely.**

DVH – DIBH VS FB



DIBH: Technology, Workflow & Dose Constraints

ABC (Active Breathing Coordinator)

Vendor: Elekta

Advantages:

- ✓ Pneumotachograph controlled
- ✓ Reproducible breath-hold volume
- ✓ Gating with precise threshold
- ✓ Low inter-fraction variability

Limitations:

- ✗ Mouthpiece required
- ✗ Claustrophobia possible
- ✗ Requires coaching time

RPM / AlignRT (Surface Guided)

Vendor: Varian / VisionRT

Advantages:

- ✓ Markerless optical tracking
- ✓ Real-time 3D surface
- ✓ No patient contact
- ✓ Rapid setup

Limitations:

- ✗ Tattoo-independent positioning
- ✗ Light sensitivity
- ✗ Higher cost

Spirometry + Visual Feedback (Self-held)

Vendor: Various / Bellows

Advantages:

- ✓ Low cost
- ✓ Widely available
- ✓ Patient empowerment
- ✓ No equipment attached

Limitations:

- ✗ Less reproducible
- ✗ Requires sustained effort
- ✗ Coaching burden

DIBH Cardiac Dose Constraints (ESTRO ACROP 2020 / UK RCR):

Mean Heart Dose: <2 Gy (aspirational) / <4 Gy (acceptable) | V25 Heart: <10% | LAD Dmax: <40 Gy | LAD Dmean: <15 Gy | V20 Ipsi Lung: <30%

Combining DIBH + HF/UHF: Practical Integration

Why DIBH Matters MORE with UHF (FAST-Forward 5 fx)

Each FAST-Forward fraction delivers 5.2 Gy — the cardiac structures receive proportionally higher biological dose per fraction. With the LQ model, 5.2 Gy/fx to the heart (α/β ~2–3 Gy for cardiac late toxicity) creates substantially higher BED than 2.67 Gy/fx. Cardiac dose reduction via DIBH therefore becomes EVEN MORE critical with UHF than with standard HF. This principle is now embedded in FAST-Forward implementation guidelines.

01

CT Simulation

Free-breathing CT first. Contour heart, LAD, predict MHD. If MHD >3 Gy → proceed to DIBH CT.

02

DIBH Coaching

2–3 practice sessions. Target: breath-hold ≥20 sec, amplitude stable ±2 mm on RPM/bellows.

03

DIBH CT Sim

ABC / SGRT. Confirm MHD reduction >30% vs FB or absolute <2 Gy. If not — reassess technique.

04

Plan Optimisation

VMAT or 3D-CRT in DIBH. FiF for dose homogeneity. Meet constraints. Adaptive if needed (EVO).

05

Treatment & IGRT

CBCT or SGRT daily. Breath-hold gating at treatment. 5 daily fractions with pre-fx coaching. Review BH trace.

POST-MASTECTOMY RT

Hypofractionation for PMRT: Evidence & Standards

Historical Context:
PMRT was long withheld from HF due to concerns over chest wall/nodal field inhomogeneity and absence of RCT data. This hesitancy is now largely resolved.

MA.20 (HF re-analysis)

Whelan et al. NEJM 2011 / HF subgroup analysis

Nodal RT + WBI with HF schedules: no excess toxicity vs conventional in loco-regional fields. Supports extending HF to PMRT + nodal volumes.

Supports HF extension

HYPORT-BC (India, CMC Vellore)

Agarwal et al. JCO 2023

N=300. 40 Gy/15 fx vs 50 Gy/25 fx for PMRT ± nodal RT. Primary endpoint: acute skin toxicity — non-inferior. LC and DFS comparable at 3 yr. Landmark Indian PMRT HF data.

Non-inferior ✅ (Indian data)

PMRT HF RCT (China)

Wang et al. Int J Radiat Oncol 2022

N=820. 43.5 Gy/15 fx vs 50 Gy/25 fx post-mastectomy with nodal RT. 5-yr LRR: 8.1% vs 8.3% (NS). Grade 2+ acute skin: similar. OS equivalent.

Non-inferior ✅

ASTRO 2022 Guideline

Smith BD et al. Pract Radiat Oncol 2022

HF (40–42.5 Gy/15–16 fx) conditionally recommended for PMRT including nodal RT in patients without implant-based reconstruction. Evidence sufficient for clinical use.

Guideline endorsed

⚠ Implant-based reconstruction: HF for PMRT with tissue expanders/implants — use with caution. Insufficient RCT data; discuss with plastic surgery. Conventional fractionation preferred if immediate reconstruction with implant.

NODAL ULTRAHYPOFRACTIONATION

5-Fraction Schedules for Loco-Regional RT: Where Are We?

Current Status: Nodal UHF is INVESTIGATIONAL. Evidence is emerging but NOT yet sufficient for routine practice outside of clinical trials. This is the next frontier.

Radiobiological Rationale

- Nodal metastases: α/β likely ~3–4 Gy (similar to primary tumour)
- LQ model predicts UHF should be equally effective for nodal disease
- Practical benefit: 1-week treatment for WBI + full nodal fields
- BUT: dose inhomogeneity in nodal volumes is a real concern with large fx

Key Concerns with Nodal UHF

⚠ Brachial plexus: Dmax constraint tighter with 5.2 Gy/fx (α/β ~2–3 Gy)

⚠ Lung V20 & heart dose — larger volumes make DIBH non-negotiable

⚠ Dose homogeneity: axillary/IMC fields harder to optimise with VMAT/5fx

⚠ No mature RCT data for nodal-only or PMRT+nodal UHF

FAST-Forward (Nodal subgroup)

Brunt et al. Lancet 2020

~20% of FAST-Forward pts had N1 disease. Subgroup: 5-yr LRR similar across arms. Underpowered for definitive nodal conclusion but reassuring signal.

PRIMETIME Trial (UK, ongoing)

CRUK / NCT04019587

40 Gy/15 fx WBI + axilla/IMC nodal RT vs conventional. Primary: late toxicity. Will provide definitive HF nodal data. UHF nodal arm not included.

5-Fx Nodal RT Pilot (Toronto)

Kirova et al. / Multiple institutional series 2022–24

26 Gy/5 fx for chest wall + nodal RT: feasibility studies. Acute toxicity acceptable. 2-yr locoregional control promising. Awaiting mature data.

Neo-FAST / UHF-PMRT (India, ongoing)

Multiple TATA/AIIMS institutional protocols 2023–25

26–28 Gy/5 fx schedules for PMRT + nodal RT in resource-constrained settings. Acute toxicity data emerging. Not yet standard of care.

Bottom Line: UHF (26 Gy/5 fx) nodal RT = promising, enrol in trials or use institutional protocols with caution + MDT consensus + DIBH mandatory.

HF (40 Gy/15 fx) nodal RT = evidence-based, use now.

OAR Constraints, Planning Pearls & Dose Schedules

Recommended Dose Schedules

Setting	Standard HF (SoC)	UHF (Investigational)	Evidence Level
PMRT chest wall only	40 Gy/15 fx (2.67 Gy/fx)	26 Gy/5 fx (5.2 Gy/fx)	HF: Level 1A | UHF: Level 2B
PMRT + axillary/SCF nodes	40 Gy/15 fx (whole field)	26 Gy/5 fx — trial only	HF: Level 1B | UHF: feasibility
PMRT + IMC	40 Gy/15 fx (DIBH mandatory)	Not recommended routinely	HF: Level 2A | UHF: insufficient
Post-BCS + full nodal RT	40 Gy/15 fx + SIB 48 Gy	Investigational (PRIMETIME)	HF: Level 1A | UHF: investigational
Boost to CW scar / tumour bed	+ 10–16 Gy / 4–8 fx seq.	SIB approach (institutional)	Expert consensus

OAR Constraints: 26 Gy/5 fx with Nodal Fields (Institutional Guidance)

OAR	Constraint (26 Gy/5 fx)	EQD2 Equivalent	Priority
Heart MHD	<2 Gy (DIBH mandatory left-sided)	~4.3 Gy EQD2	MANDATORY
Brachial plexus Dmax	<26 Gy (= prescription dose)	~43 Gy EQD2 (α/β 3)	CRITICAL
Spinal cord Dmax	<20 Gy	~40 Gy EQD2 (α/β 2)	MANDATORY
LAD mean (left-sided)	<8 Gy | Heart V15Gy <15%	~17 Gy EQD2	High
Ipsilateral lung V20	<25% (BCS) / <30% (PMRT)	Standard	High
Ipsilateral lung V5	<60% | Contralateral lung V5 <15%	Low-dose bath	Moderate

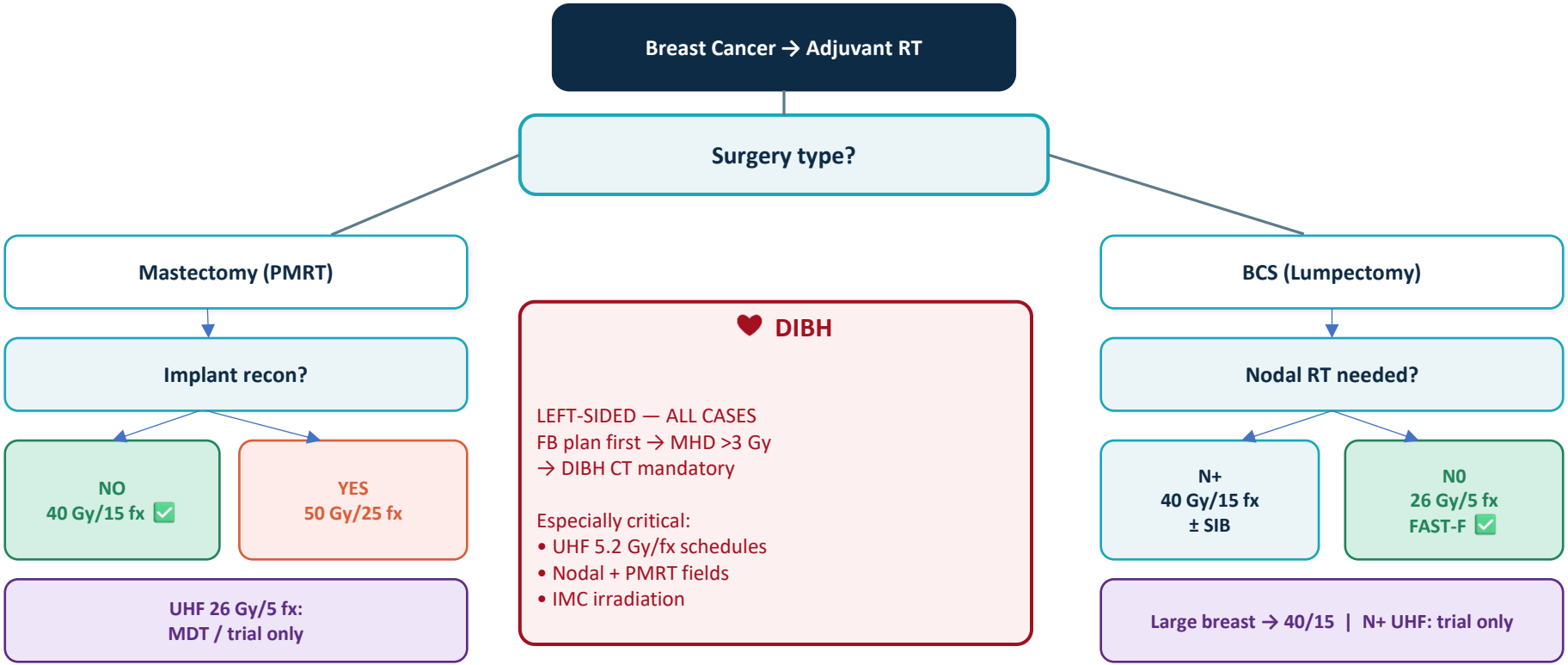
Planning Pearls: VMAT preferred. DIBH non-negotiable left-sided. Brachial plexus = dose-limiting for SCF fields. SIB preferred over sequential boost. Validate on phantom before first patient.

OAR Dose Constraints (ESTRO ACROP 2020 / UK RCR)

OAR	Standard HF (40 Gy/15 fx)	UHF (26 Gy/5 fx)	Priority
Heart MHD	<4 Gy (aspirational <2 Gy)	<2 Gy (DIBH mandatory)	MANDATORY
LAD mean (left-sided)	<15 Gy	<8 Gy	High
Ipsilateral lung V20	<20–25%	<25% (BCS) / <30% (PMRT)	High
Brachial plexus Dmax	<40 Gy (EQD2)	<26 Gy (= prescription dose)	CRITICAL (UHF)
Spinal cord Dmax	<40 Gy (EQD2)	<20 Gy	MANDATORY

CLINICAL DECISION ALGORITHM

Surgery → Fractionation → DIBH Selection



Future Directions & Unanswered Questions

Ongoing

FAST-F + Boost

SIB with 5 fx (e.g., 26+30 Gy/5) is the next frontier. IMPORT HIGH SIB evidence may extend to UHF. Multiple trials ongoing (PRIMETIME).

Awaited

UHF + Nodal RT

FAST-Forward nodal data insufficient. PRIMETIME trial will address HF nodal RT. UHF nodal RT remains investigational.

Emerging

DIBH + ART

Online adaptive RT (Elekta EVO, Elekta Unity MR-Linac) for breath-hold day-to-day anatomy changes. Reduces CTV–PTV margins. Early feasibility data promising.

Established

Partial Breast RT

APBI 5-fraction schedules (30 Gy/5 fx, alternate days) — IMPORT LOW, RAPID trial. Complements whole-UHF for early BC. Select candidates well.

Scaling

SGRT Universal

Surface-guided RT to replace tattoos + improve DIBH precision. Reduces inter-fraction positioning errors. Set-up time ↓ especially relevant with 5-fx (less margin for error).

Active

AI Contouring

Auto-segmentation of heart, LAD, breast structures accelerates DIBH dosimetry review. Must be validated per site anatomy and MHD threshold protocols.

Key Take-Home Messages

1. Hypofractionation (40 Gy/15 fx or 42.5 Gy/16 fx) is the STANDARD OF CARE for whole-breast RT. Conventional 50 Gy/25 fx has no remaining role as a default.

2. FAST-Forward 26 Gy/5 fx is non-inferior to 40 Gy/15 fx for local control. It is guideline-endorsed (ASTRO, ESTRO) and should be offered to eligible N0-N1 patients — 1-week treatment.

3. Nodal RT with HF (40 Gy/15 fx) is supported by evidence. UHF nodal RT remains investigational — do not offer outside protocols.

4. DIBH is mandatory for left-sided breast cancer when FB MHD >3–4 Gy. With UHF, cardiac BED is HIGHER per fraction — DIBH is even more critical with 5-fraction schedules.

5. Integrate DIBH + UHF systematically: plan FB CT first → check MHD → proceed to DIBH CT if threshold met → treat with gating. Elekta EVO / SGRT workflows are well-suited for this.

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