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Fractionation in early breast cancer radiotherapy

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Radiotherapy in Breast Cancer

- The **traditional dose** and fractionation radiotherapy regimen of **50 Gy in 25 fractions** for early breast cancer has been used by radiation oncologists for a long period of time (the Danish Breast Cancer Group (since 1982)).

- Four randomised trials testing fraction sizes in the range 2.7–3.3 Gy have reported 10-year follow up in ≈ 8000 patients, had provided robust estimates of **α/β in the range of 3 Gy**.

Radiotherapy in Breast Cancer

- Over the past two decades, **moderate hypofractionation** (40–42·56 Gy in 15–16 fractions over 3 weeks) has been shown to be **at least as effective** with respect to local control and survival with similar, if not decreased, **early and late normal tissue effects as** conventionally fractionated whole breast irradiation.

ASTRO: moderate hypofractionation (HF), defined as daily doses ranging from 265 to 330 cGy

The DBCG HYPO Trial (long-term follow-up)

1,854 node-negative patients [invasive: 1,608 in situ:246]

- 40 years of age
- BCS without immediate reconstruction
- Median age: 59 years (range, 41-83 years)
- Median CTVp breast: 640 mL

R 1:1

50 Gy in 25 fr (n=937)

The 3-y rate of grade 2-3 induration

11.8%

Stratification :

Age, breast size, laterality, tumor size, grade, subtype, systemic therapies

40 Gy in 15 fr (n=917)

9%

PRIMARY ENDPOINT

- breast induration (considered a marker for fibrosis, which is a histologic finding)

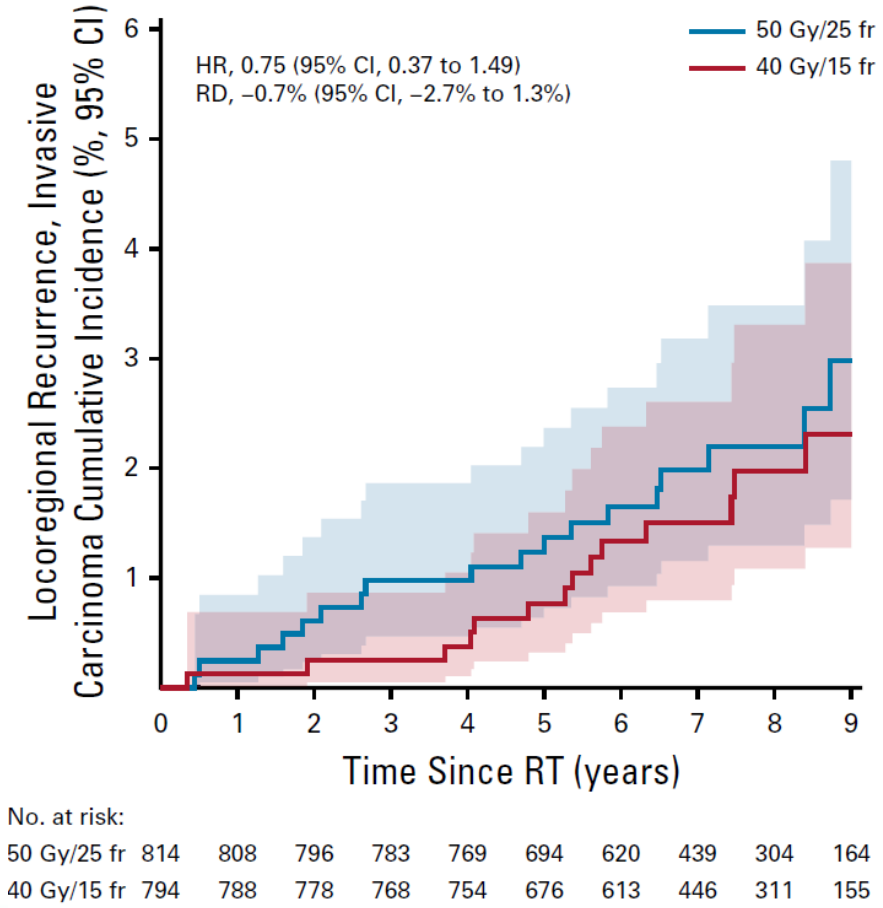
SECONDARY ENDPOINTS

- telangiectasia, dyspigmentation, scar appearance, and edema

The DBCG HYPO Trial (long-term follow-up)

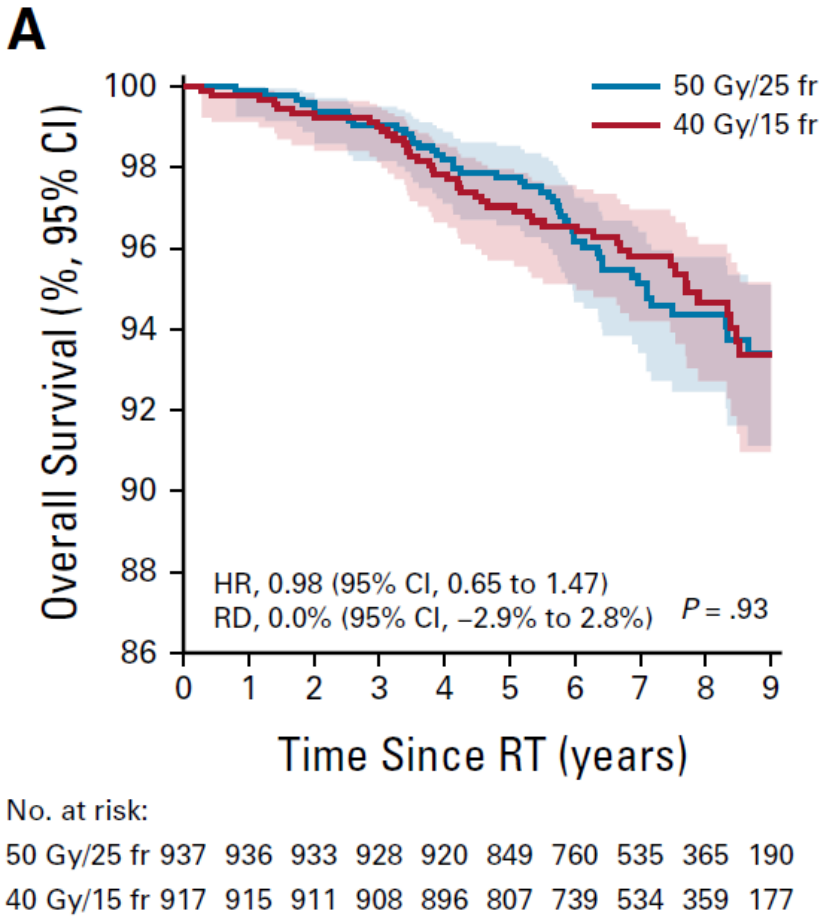
- Overall, the normal tissue effects were low and either similar or less severe in the 40-Gy group.
- Approximately 90% and 85% of patients reported excellent or good cosmetic outcomes at both 3 and 5 years.

The DBCG HYPO Trial (long-term follow-up)



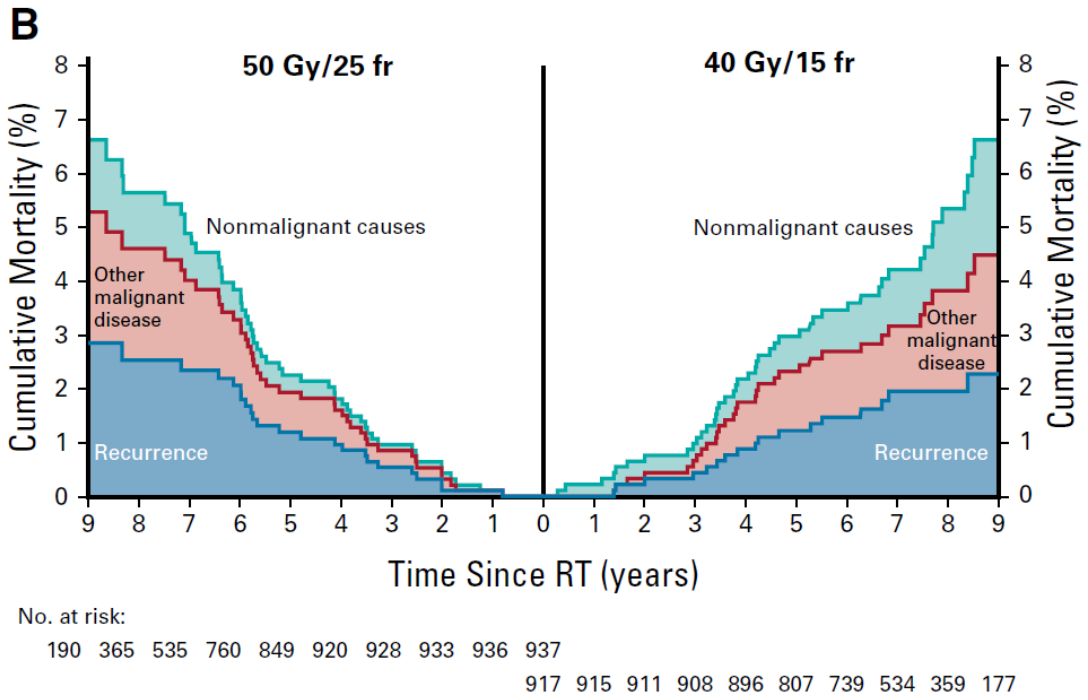
- A median follow-up of 7.26 years
- No significant difference
  - including 19 patients in the 50-Gy group and 14 patients in the 40-Gy group (hazard ratio [HR], 0.75; 95% CI, 0.37 to 1.49; P = .41)
  - 8 of these recurrences (50-Gy group [n = 4]; 40-Gy group [n = 4]) were considered new primary tumors and treated accordingly; the rest were treated as true local recurrences

The DBCG HYPO Trial (long-term follow-up)



- No significant difference
  - At 9 years, the overall survival rate was 93.4% in the 50-Gy group and 93.4% in the 40-Gy group (risk difference, 0%; 95% CI, −2.9% to 2.8%; P = .93;

The DBCG HYPO Trial (long-term follow-up)



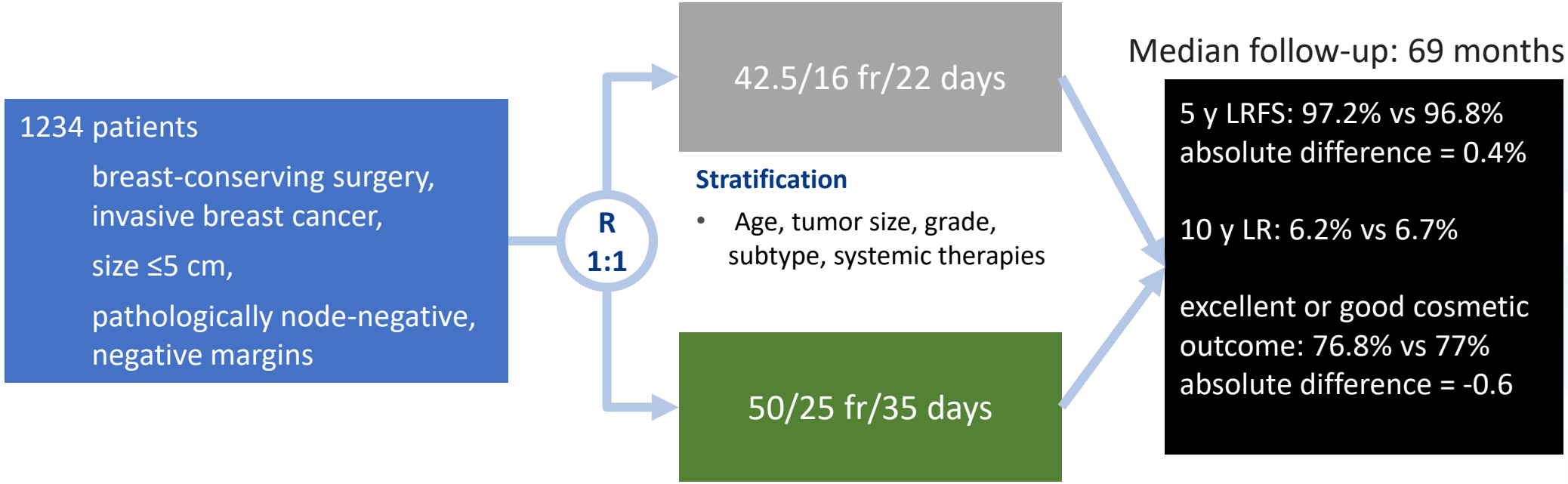
- No significant difference
  - died without cancer: 22 patients who
    - cardiac disease; 5 patients died

    50-Gy group [n = 2],

    40-Gy group [n = 3]

    two right-sided and three left-sided heart failures

The Ontario Clinical Oncology Group trial



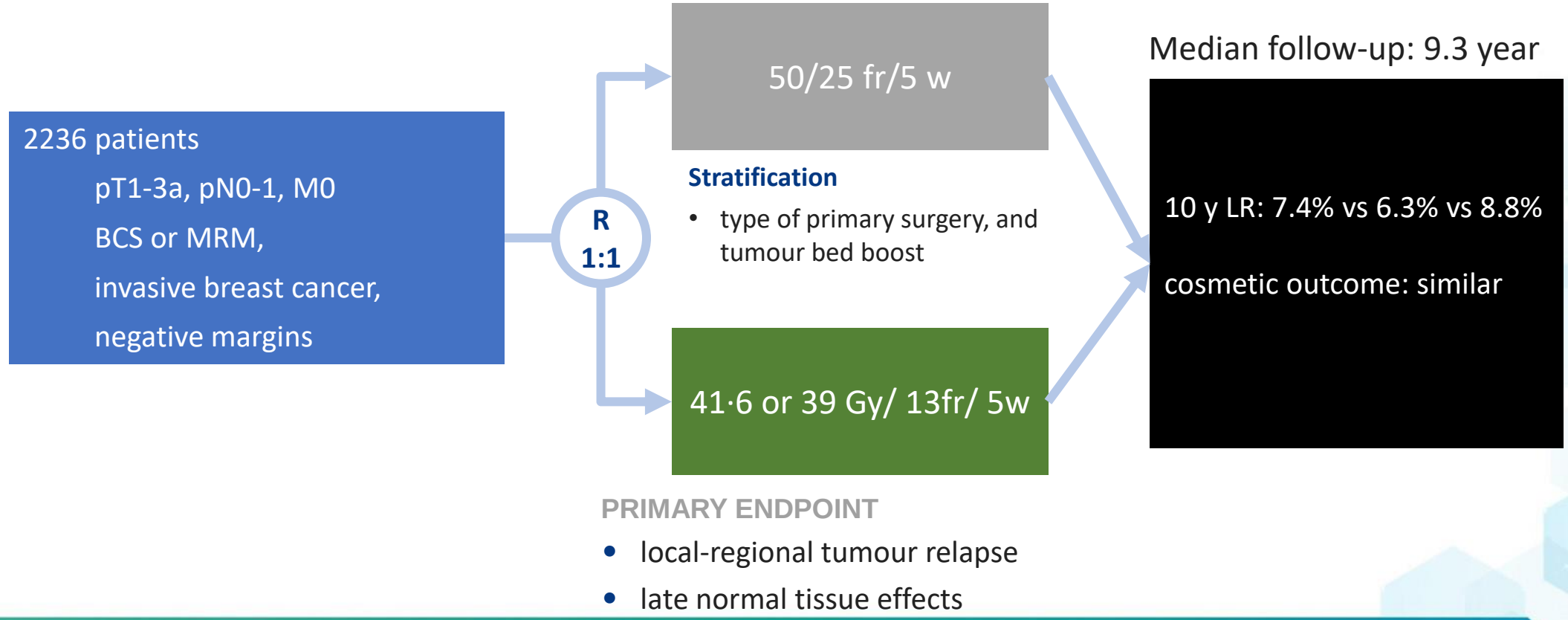
PRIMARY ENDPOINT

- local recurrence of invasive disease in the treated breast

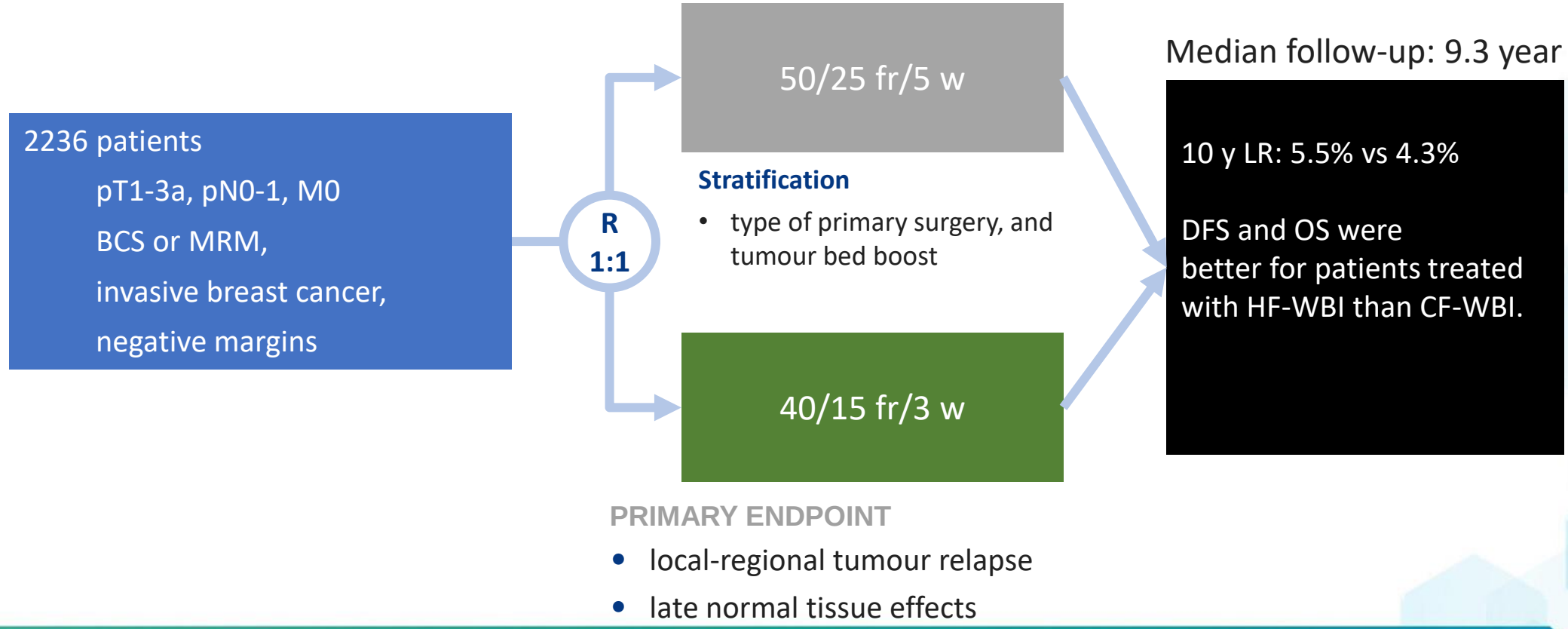
SECONDARY ENDPOINTS

- cosmetic outcome [EORTC Cosmetic Rating System]

The UK Standardisation of Breast Radiotherapy (START-A)



The UK Standardisation of Breast Radiotherapy (START-B)



The UK Standardisation of Breast Radiotherapy (START)

- The late effects of **breast appearance**, **breast edema** or **hardness**, or **skin changes** were generally **equal or better** with hypofractionation, and there were **no significant differences** in late effects of **rib fracture** or **ischemic heart disease**.

Local relapse in randomised trials testing hypofractionated radiotherapy after BCS for early breast cancer

Trial	Randomisation (Gy/fraction)	% 5 year local relapse (95% CI)	% 10 year local relapse (95% CI)
START-A	50.0/25	3.4 (2.3–5.1)	6.7 (4.9–9.2)
	41.6/13	**3.1 (2.0–4.7)**	**5.6 (4.1–7.8)**
	39.0/13	4.4 (3.1–6.2)	8.1 (6.1–10.7)
START-B	50.0/25	**3.3 (2.4–4.6)**	**5.2 (2.7–5.2)**
	40.0/15	1.9 (1.2–3.0)	3.8 (2.7–5.2)
Ontario	50.0/25	3.2[a]	6.7[b]
	42.5/16	2.8[a]	6.2[b]

[a]Absolute difference 0.4% [95% CI (–1.5 to +2.4%)].
[b]Absolute difference 0.5% [95% CI (–2.5 to +3.5%)].

Clinically assessed moderate or marked adverse effects for patients treated by BCS and hypofractionated radiotherapy in randomised trials

Trial	Randomisation (Gy/fraction)	% breast shrinkage at 10 year (95% CI)	% excellent or good breast cosmesis at 10 year (95% CI)
START-A	50.0/25	34.2 (29.8–39.2)	
	41.6/13	**31.4 (27.2–36.0)**	
	39.0/13	30.0 (25.7–34.8)	
START-B	50.0/25	31.2 (27.9–34.9)	
	40.0/15	**26.2 (23.1-29.6)**	
Ontario	50.0/25		71.3 [a]
	42.5/16		69.8[a]

[a]Absolute difference 1.5% [95% CI (−6.9 to +9.8)]

- Radiobiologic models based on trial data suggested an α/β ratio of 350-400 cGy for late radiation effects to the breast and an α/β ratio for breast cancer control of approximately 350 cGy.

- These findings support the conceptual model that CF-WBI does not provide an incremental benefit with regard to either tumor control or normal tissue toxicity compared to HF-WBI.
- In light of the totality of the evidence, the most guidelines favored HF-WBI regimens of 4250 cGy in 16 fractions or 4000 cGy in 15 fractions, as these are the only two regimens that were administered on consecutive treatment days in the randomized literature.

Guideline adaptation (ASTRO, 2018)

Practical Radiation Oncology (2018)

practical radiation oncology
pro

Radiation Therapy for the Whole Breast: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline

Table 1. Patients for whom consensus supports use of hypofractionated WBI: A comparison of the 2011 and 2018 ASTRO Guidelines*

Factor	*2011 Guideline*	*2018 Guideline*
Age	50 years and older	Any age
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

For women with invasive breast cancer receiving WBI **with or without inclusion of the low axilla**, the **preferred** dose-fractionation scheme is HF-WBI to a dose of 4000 cGy in 15 fractions or 4250 cGy in 16 fractions.

- Recommendation strength: Strong
- Quality of evidence: High
- Consensus: 100%

Guideline adaptation (NCCN, 2022)

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should be routinely utilized to delineate target volumes and adjacent organs at risk.
  - Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons ± electrons.
  - Improved homogeneity of the target dose and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated RT (IMRT).
  - Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
  - Verification of treatment setup consistency is done with weekly imaging. When using certain techniques (ie, prone breast), more frequent imaging may be appropriate. Standard utilization of daily imaging is not recommended.
  - When treating the internal mammary nodes, dose-volume histograms (DVHs) should be used to evaluate dose constraints, dose to normal tissues (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated.

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; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - A boost to the tumor bed is recommended in patients at higher risk for recurrence. 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 delivered as 5 (once-a-week) fractions may be considered in select patients aged >50 years following BCS with pTis/T1/T2/N0, though the optimal fractionation for the boost delivery is unknown for this regimen.[a,b]
- 3-D planning to minimize inhomogeneity and exposure to heart and lung is essential when using this regimen.

Guideline adaptation (ESTRO, 2022)

THE LANCET
Oncology

REVIEW | VOLUME 23, ISSUE 1, E21-E31, JANUARY 2022

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

Icro Meattini, MD • Carlotta Becherini, MD • Prof Liesbeth Boersma, MD • Orit Kaidar-Person, MD • Gustavo Nader Marta, MD • Angel Montero, MD • et al. Show all authors • Show footnotes

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	Consensus agreement	Strength
1. Whole breast irradiation		
1a. Moderate hypofractionated whole breast irradiation should be offered regardless of:		
I. Age at breast cancer diagnosis	91·3%	Strong consensus
II. Pathological tumour stage	91·3%	Strong consensus
III. Breast cancer biology	91·3%	Strong consensus
IV. Surgical margins status	100%	Unanimous consensus
V. Tumour bed boost	100%	Unanimous consensus
VI. Breast size	91·3%	Strong consensus
VII. Invasive or pre-invasive DCIS disease	91·3%	Strong consensus
VIII. Oncoplastic breast conserving surgery	91·3%	Strong consensus
IX. Use of systemic therapy	95·6%	Strong consensus

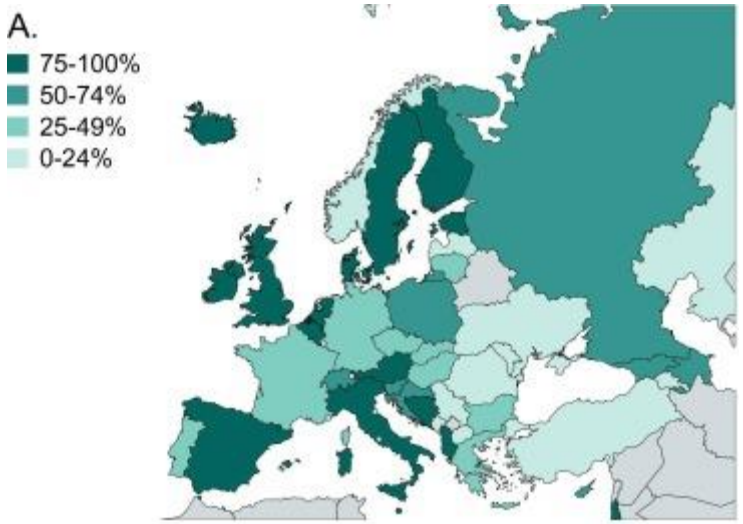
40 Gy in 15 fractions is currently standard of care for all UK patients prescribed adjuvant local or local-regional radiotherapy for operable breast cancer.

If a tumour bed boost dose is indicated in patients with high risk features, an additional 13.5 Gy in five fractions of 2.7 Gy delivers the equivalent of 14 Gy in seven fractions of 2 Gy, assuming an α/β of 3 Gy.

[There is **no indication** to use more than 15 fractions for the breast, chest wall or nodal areas for standard adjuvant treatment.]

What real world data say…

While the current standard of care in the adjuvant whole breast irradiation of early stage breast cancer is moderate hypofractionation, studies have shown that this approach is not implemented in routine clinical practice.



HFRT was chosen as the preferred schedule for whole breast irradiation by 54.7% and for WBI with regional nodes irradiation by 28.7% of radiation oncologists (Ratosa et al 2021)

And the era of Ultrahypofractionated WBRT…

- Recently, 10-year results from the FAST and 5-year results from the FAST-Forward trial evaluating adjuvant whole-breast radiotherapy in 5 fractions over 5 weeks or 1 week have been published.

The FAST Trial (Ten-Year Results)

Median follow-up: 9.9 y

915 patients
- invasive early breast cancer
- age ≥ 50 years,
- tumor size < 3 cm,
- axillary node negative,
- BCS with complete microscopic resection,

50 Gy in 25 fractions of 2.0 Gy

30 Gy in 5 once-weekly fractions of 6.0 Gy

28.5 Gy in 5 once-weekly fractions of 5.7 Gy

ipsilateral breast LR: 11
- 50 Gy: 3;
- 30 Gy: 4;
- 28.5 Gy: 4

Deaths: 96
- 50 Gy: 30;
- 30 Gy: 33;
- 28.5 Gy: 33

PRIMARY ENDPOINT

- photographic breast appearance

SECONDARY ENDPOINTS

- ipsilateral disease in the breast (relapse or new primary)

The FAST Trial (Ten-Year Results)

- ORs for any moderate/marked physician-assessed breast NTE (shrinkage, induration, telangiectasia, edema):
  - 30 Gy: 2.12 ($P < .001$)
  - **28.5 Gy**: 1.22

The FAST-Forward Trial (Five-Year Results)

The 5 fraction schedules required
EPID verification for each fraction

Median follow-up: 71.5 m

4096 patients
- invasive early breast cancer
- age ≥ 18 years,
- pT1–3, pN0–1, M0,
- BCS or mastectomy (reconstruction allowed)

40 Gy in 15 fractions of 2·67 Gy over 3 weeks)

27 Gy in five fractions of 5·4 Gy over 1 week

26 Gy in five fractions of 5·2 Gy over 1 week

ipsilateral breast LR: 79
- 40 Gy: 31;
- 27 Gy: 27;
- 26 Gy: 21

LR HRs vs 40Gy (p<0.001):
- 27 Gy: −0.3%;
- 26 Gy: -0.7%

Excluded the lowest-risk patients (aged ≥65 years, pT1, grade 1 or 2, ER +, HER2 negative, pN0, M0)

nodal radiotherapy was **not** allowed in the main study

PRIMARY ENDPOINT
- ipsilateral breast tumour relapse

SECONDARY ENDPOINTS
- late normal tissue effects

The FAST-Forward Trial (Five-Year Results)

- Patient and photographic assessments showed **higher normal tissue effect risk** for **27 Gy** versus 40 Gy but not for 26 Gy versus 40 Gy.

- FAST-Forward results confirm that 26 Gy in five fractions is as effective and safe as an international standard 15-fraction regimen after primary surgery for early breast cancer.

- The 1-week schedule has major benefits over the 3-week or 5-week regimens in terms of convenience and cost for patients and for health services globally.

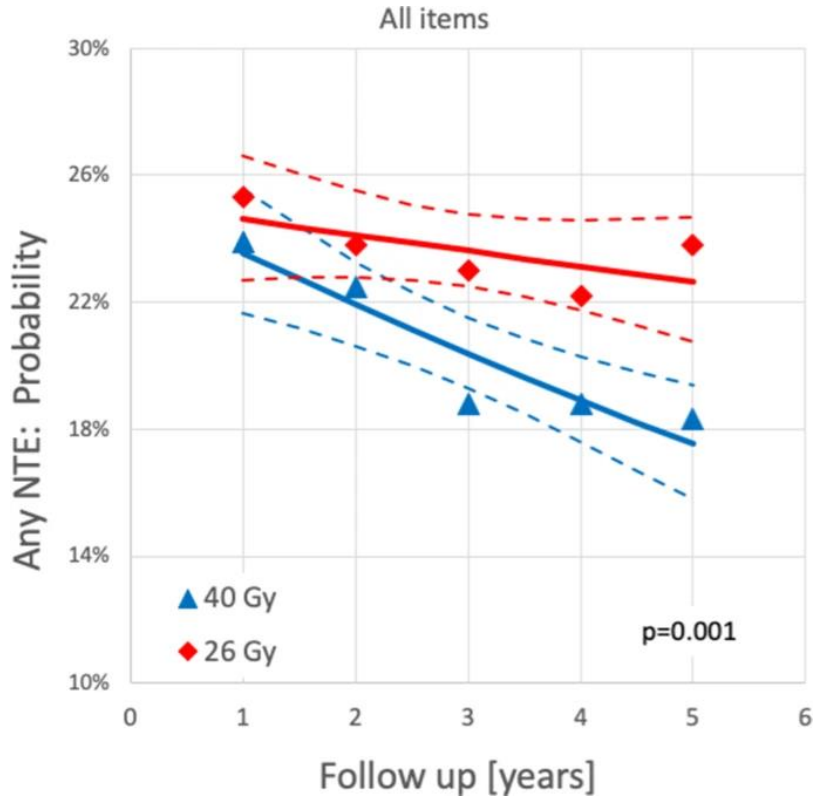
Can Ultrahypofractionated WBRT be used in all centers…

Yes, **if** ….

- EPID verification for each fraction
- breath-hold technique is available

Re-analysis of the FAST-Forward data regarding late toxicity

Breast Cancer Expert Panel of the German Society of Radiation Oncology



Binary logistic regressions showed significant differences **in favor of** the **standard arm** for induration, telangiectasia and edema as well as for the sum of all NTE

The RR of the individual observations only reached significance ($p < 0.05$) **after 3 and more** years of follow-up for breast induration and edema as well as the sum of all NTE, suggesting that **clinically relevant disadvantages may become apparent with longer follow-up**.

Re-analysis of the FAST-Forward data regarding late toxicity

Breast Cancer Expert Panel of the German Society of Radiation Oncology

Final Conclusion

The difference between the standard arm and the 26 Gy of the FAST-Forward trial concerning moderate or marked late effects increased with longer follow-up in disadvantage of the experimental arm for most items.

For now, moderate hypofractionation with 40–42.5 Gy over 15–16 fractions remains **the standard of care** for the majority of patients with breast cancer who undergo whole-breast radiotherapy without regional nodal irradiation after breast-conserving surgery.

Take home messages…

- **Moderate hypofractionation** is **the standard of care** patients with breast cancer
- What about **conventional whole breast irradiation**?
- And finally, **Ultrahypofractionated whole breast irradiation… [to be continued!]**