

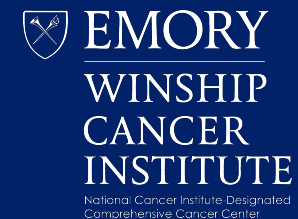


ULTRA-SHORT RADIATION FOR EARLY-STAGE BREAST CANCER: ARE 5 TREATMENTS THE NEW STANDARD?

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National Cancer Institute Designated
Comprehensive Cancer Center



Disclosures

- Emory
- NCI
- Genentech
- Pfizer
- V Foundation
- BioAscend
- MJH Life Sciences
- OncoHealth
- There will be no discussion of off-label drug or device use or references to proprietary technology

OBJECTIVE

1. To determine the efficacy and safety of ultrashort radiation treatment regimens in breast cancer patients
2. To identify which breast cancer patients are appropriate candidates for 5 radiation treatments to the whole breast

BACKGROUND

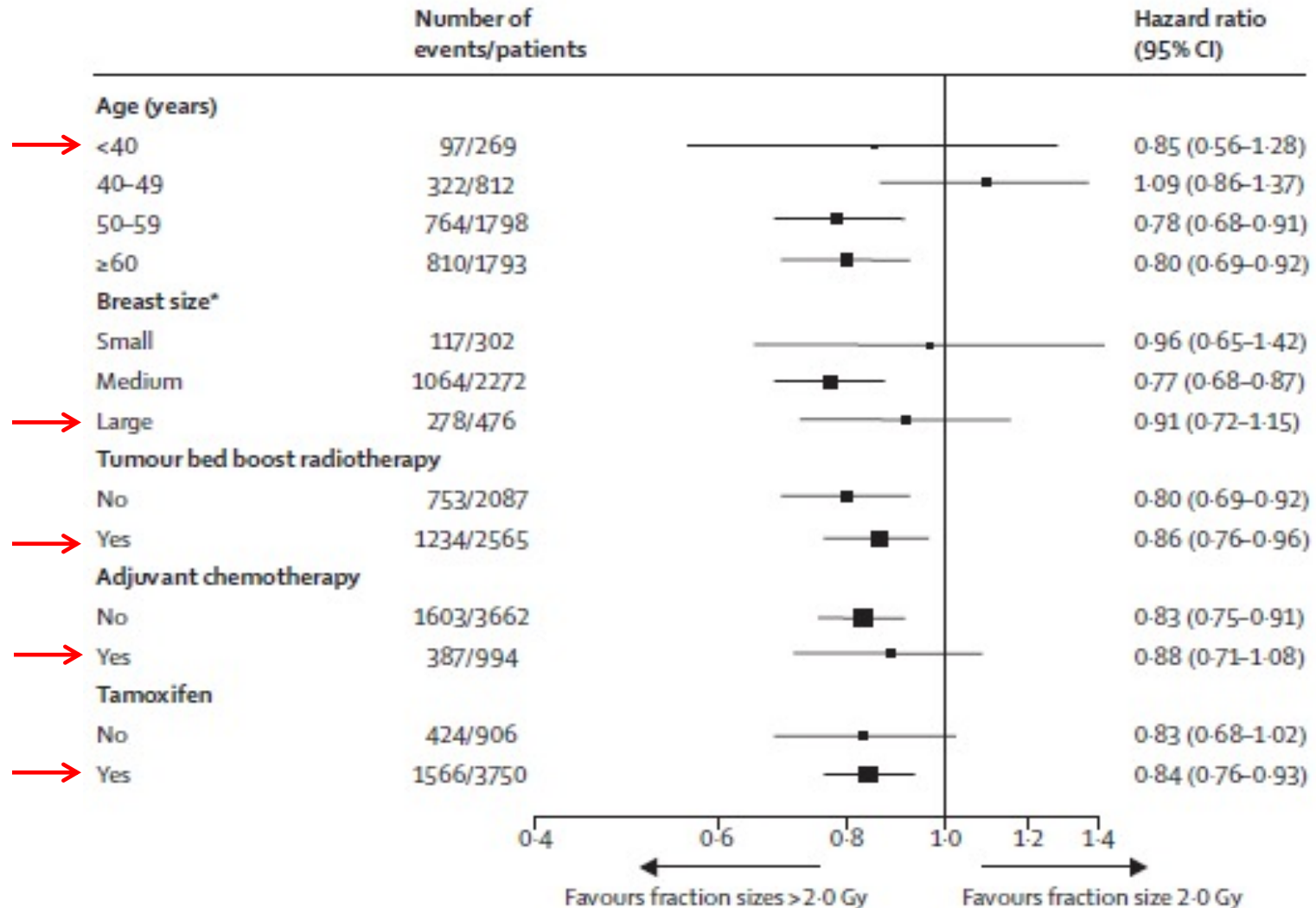
- Hypofractionation refers to radiation treatment in which the total dose of radiation is divided into large doses (usually doses ≥ 2.5 Gy per fraction) per treatment
- Treatment is given once a day or less often (e.g., once a week)
- Hypofractionated radiation therapy is given over a shorter period of time (fewer days or weeks) than standard radiation therapy (1.8 Gy to 2.0 Gy per day) traditionally given over 5-6 weeks

Larger daily doses were previously believed to cause significant normal tissue toxicity

WHOLE BREAST HYPOFRACTIONATION SEMINAL TRIALS

Trial	Years of Accrual	No. of Patients	F/U (years)	Radiation Dose	Local Recurrence with SWBI (%)	Local Recurrence with AWBI (%)	Toxicity
Ontario Oncology Group	1993-1996	1,234	12	42.56 Gy/16 fx 50 Gy/25 fx	6.2	6.7	No significant difference cosmetic outcomes (71.3% SWBI v 69.8% HWBI)
START-A	1999-2002	2,236	9.3	50 Gy/25 fx 41.6 Gy/13 fx 39 Gy/13 fx (all over 5 weeks)	6.7	5.6 8.1	No difference 50 Gy, 41.6 Gy with moderate or marked normal tissue effects; reduced induration/telangiectasia/edema with 39 Gy v 50 Gy
START-B	1999-2001	2,215	10	50 Gy/25 fx 40 Gy/15 fx	5.2	3.8	Breast shrinkage, telangiectasia, and edema significantly lower with 40 Gy

META-ANALYSIS OF MODERATE/MARKED NORMAL TISSUE EFFECTS



Hypofractionation associated with similar or less normal tissue changes than conventional fractionation

Trials A & B: Other late adverse events

	Trial A			Trial B	
	50Gy	41.6Gy	39Gy	50Gy	40Gy
Symptomatic rib fracture	5 (0.7%)	7 (0.9%)	9 (1.2%)	17 (1.5%)	23 (2.1%)
Symptomatic lung fibrosis	5 (0.7%)	9 (1.2%)	8 (1.1%)	19 (1.7%)	18 (1.6%)
Ischaemic heart disease [left-sided tumours]	17 (2.3%) [8]	10 (1.3%) [4]	9 (1.2%) [5]	25 (2.3%) [10]	22 (2.0%) [11]
Cardiac-related deaths [left-sided tumours]	11 (1.5%) [7]	16 (2.1%) [12]	9 (1.2%) [2]	13 (1.2%) [8]	5 (0.4%) [3]
Brachial plexopathy	0	1 (0.1%)	0	0	0

Haviland et al. Lancet Onc 2013;14:1086-94

COMMON PATIENT CHARACTERISTICS IN CLINICAL TRIALS SUPPORTING HYPOFRACTIONATION

- 80% had tumors <3.0 cm
- ~70% were node negative
- ~70% had low or intermediate grade tumors
- 85% treated with breast conserving surgery
- 85% breast only XRT (no regional nodal XRT)
- ~50% did not receive a boost
- 65% did not receive chemotherapy
- ~80% received tamoxifen

2018 ASTRO GUIDELINE FOR WHOLE BREAST RADIOTHERAPY

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

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
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

“Strong” recommendation for Hypofractionated Whole Breast Irradiation regardless of tumor grade, laterality, systemic therapy, and breast size for patients needing whole breast treatment without regional nodal irradiation

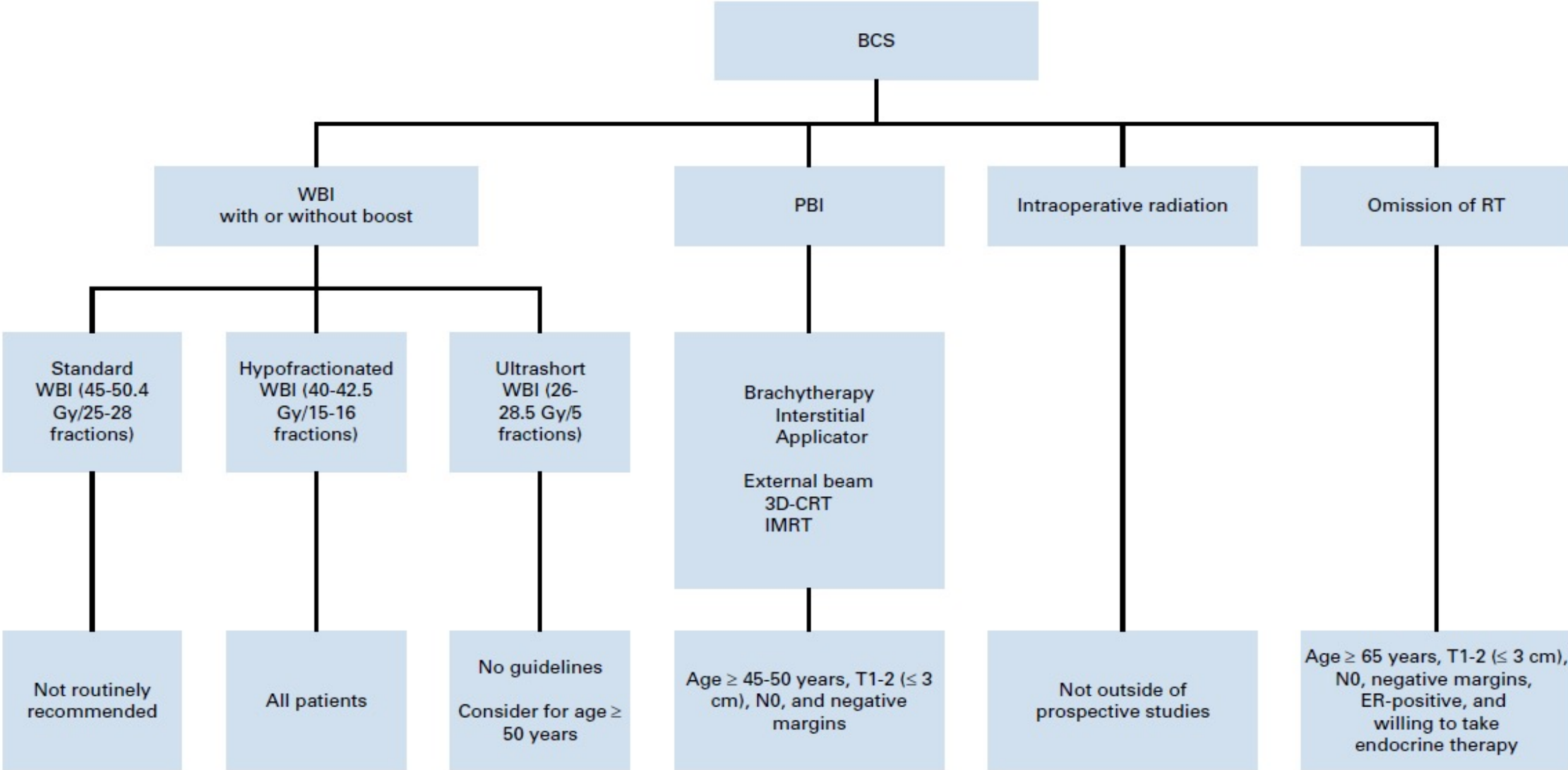
Smith et al. PRO 2018

STANDARD HYPOFRACTIONATED WHOLE BREAST IRRADIATION IN 2018

40 Gy in 15 fractions or 42.6 Gy in 16 fractions with or without a boost

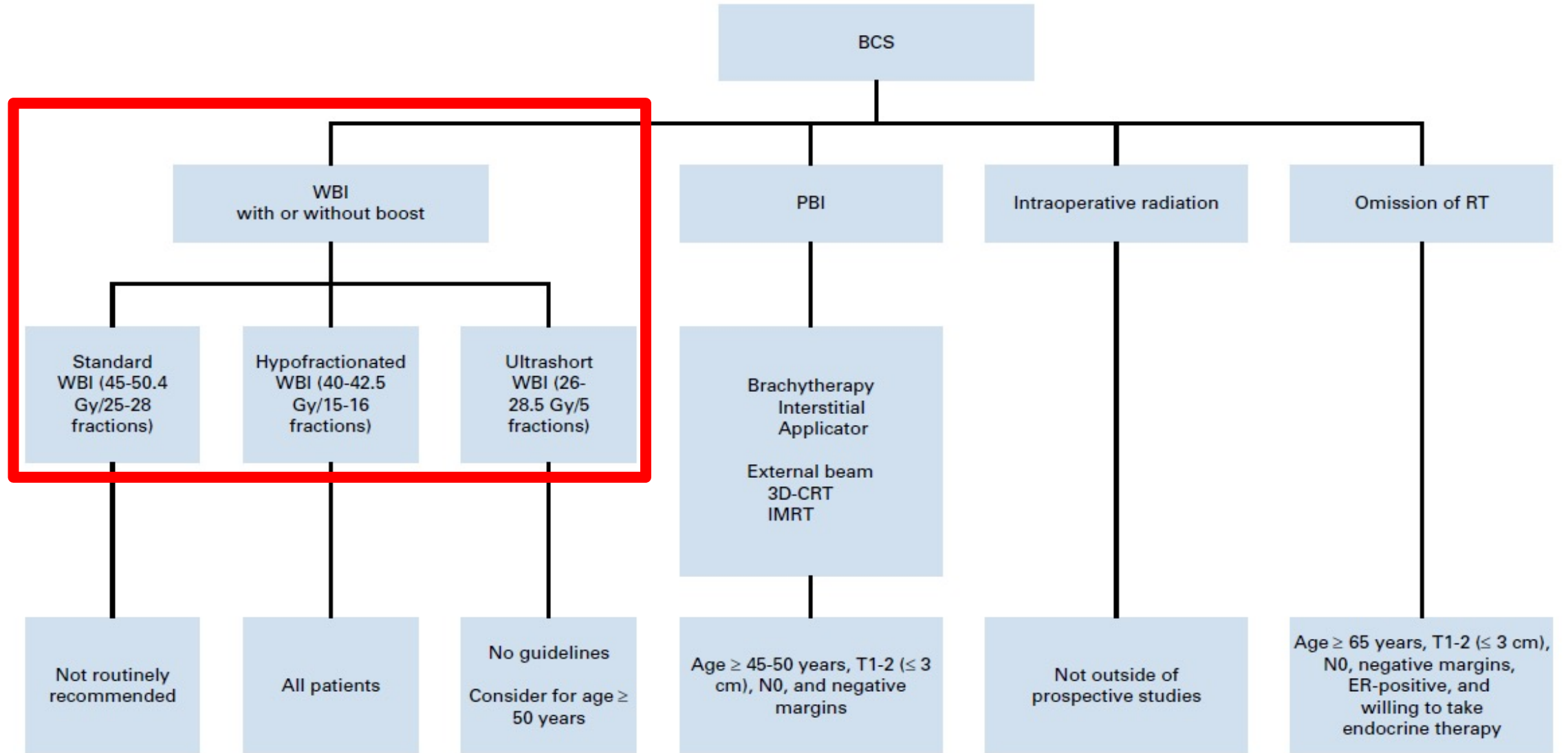
Can we further decrease the number of radiation treatments for patients with early-stage breast cancer?

Radiation Treatment Options in Early-Stage Breast Cancer



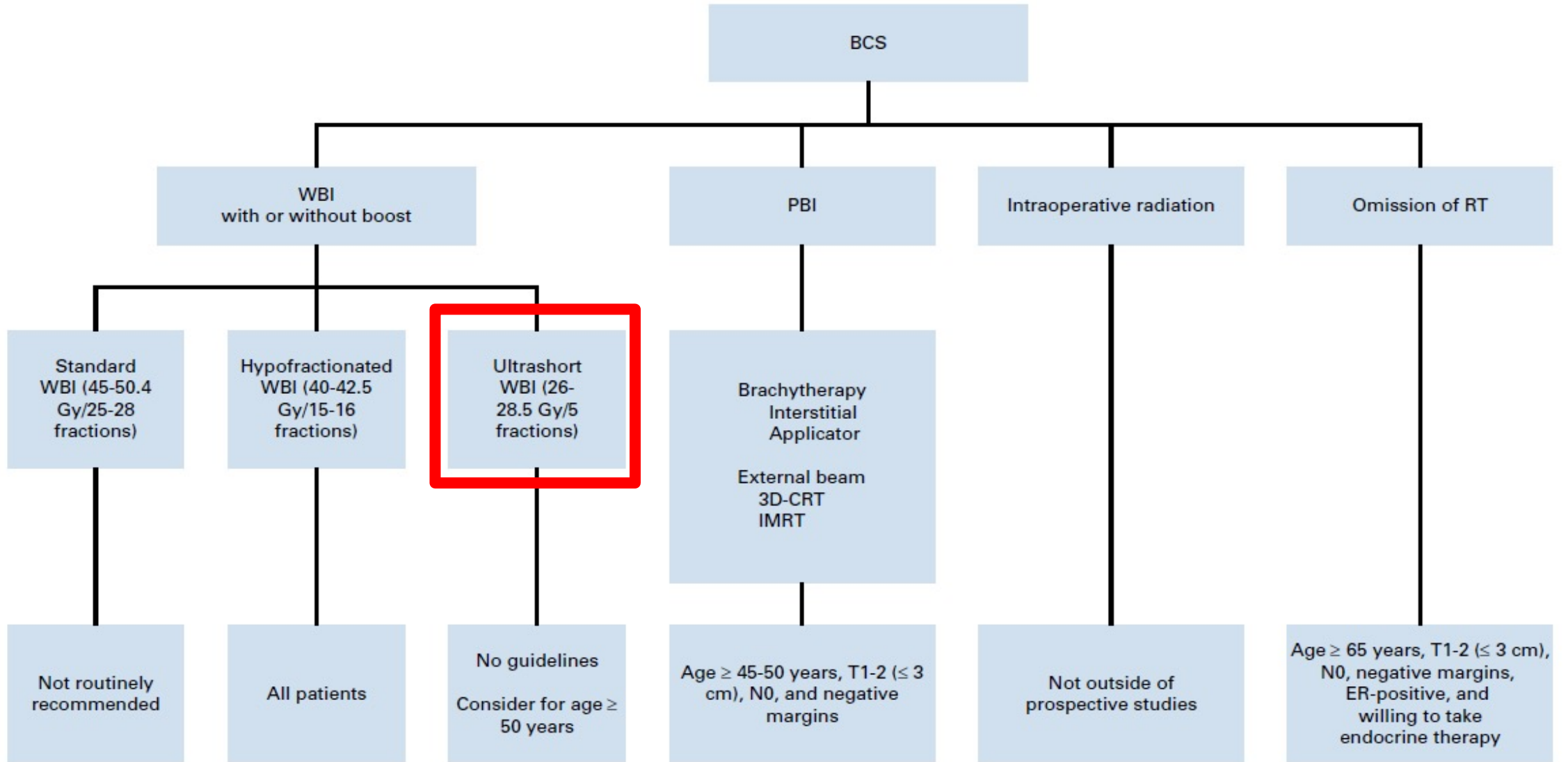
Shah et al. *JCO Oncol Practice* (2021); 17(12)

Radiation Treatment Options in Early-Stage Breast Cancer



Shah et al. *JCO Oncol Practice* (2021); 17(12)

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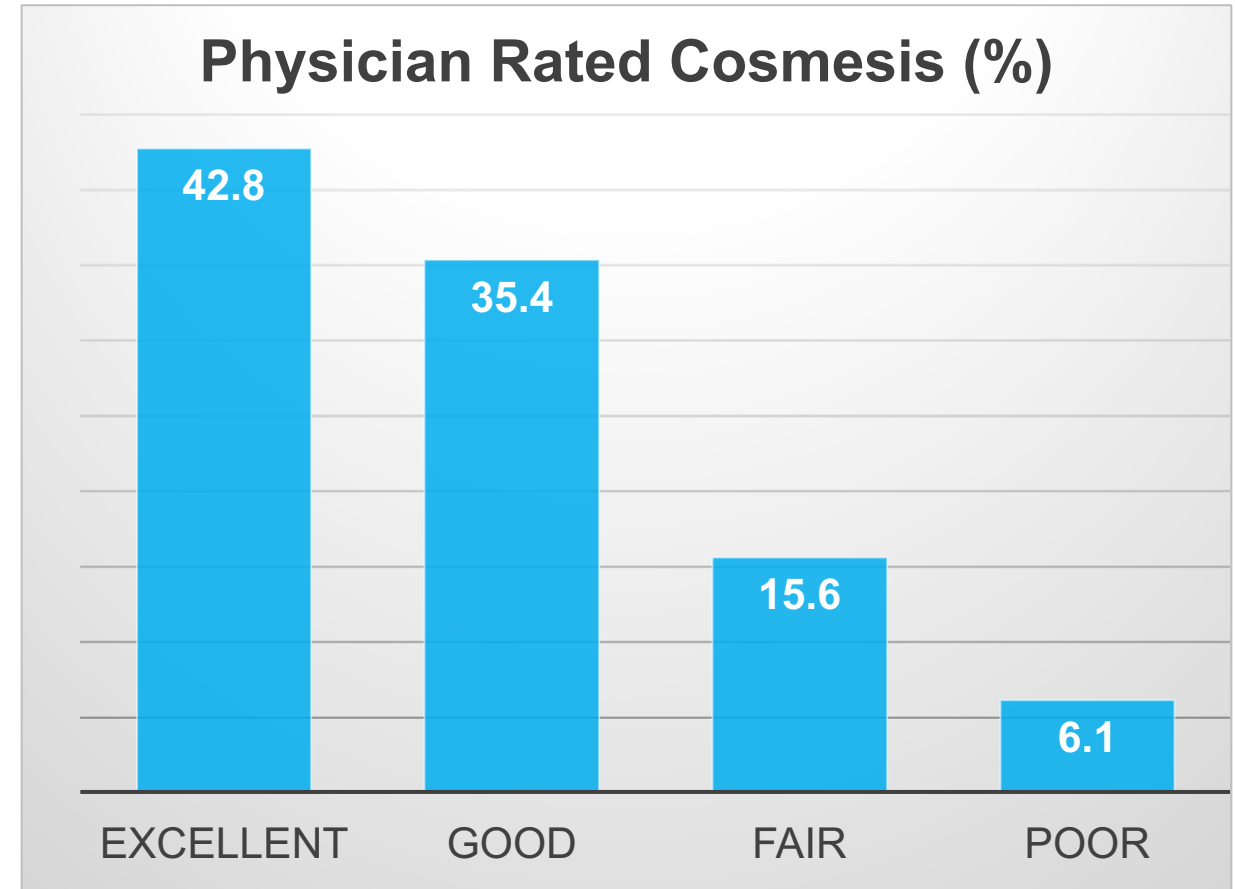
UNIVERSITY OF LOUISVILLE PHASE II TRIAL

- Phase II study of 30 Gy in 5 fxns (n=80), protocol changed to 28.5 Gy in 5 fxns (n=78) to the whole breast **given once a week**
- Stage 0-II status post breast conserving surgery
- Patients reside in rural location, transportation difficulties or financial hardship
- N=158 patients from 2011-2015
- Median follow-up: 4.4 years
- 7-year ipsilateral breast tumor recurrence rate of 6%
- 3.8% developed Grade 3 acute toxicities, No grade 4 acute toxicities

Eldredge-Hindy et al. *Ann Surg Oncol* (2021); 28:5880-5892

UNIVERSITY OF LOUISVILLE PHASE II LATE TOXICITIES

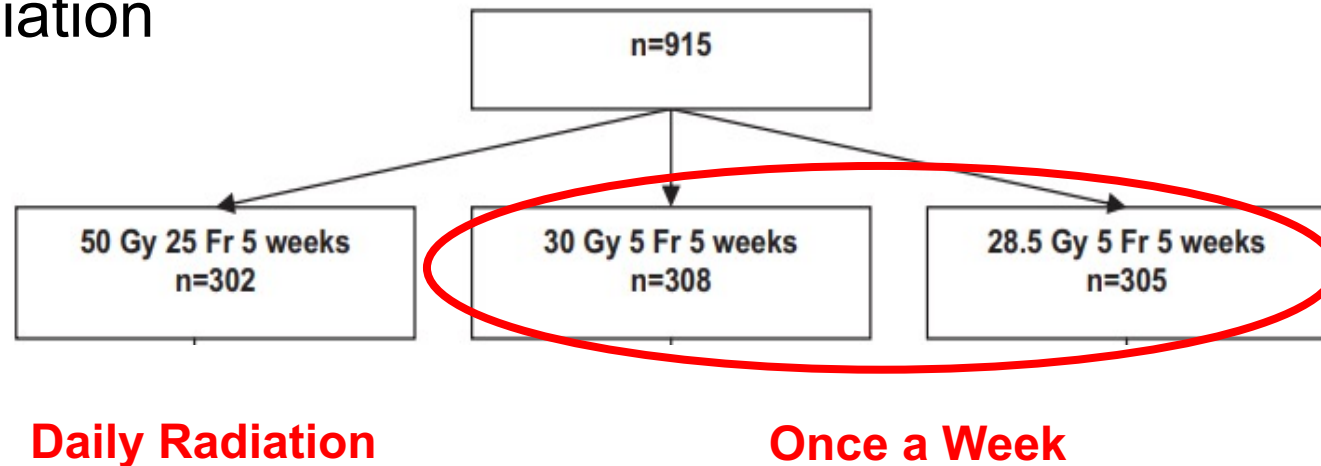
- Grade 2 or higher late soft tissue changes (25%), pain (14%), and breast/arm lymphedema (11%)
- Grade 3 (13%):
 - Grade 3 Breast shrinkage (n=10)
 - Grade 3 fibrosis (n=7)
- One patient with grade 4 cardiac toxicity (arrhythmia and non-ischemic cardiomyopathy)
- No grade 5 events



Eldredge-Hindy et al. *Ann Surg Oncol* (2021); 28:5880-5892

UK FAST

- Phase III Trial of whole breast irradiation
- Age \geq 50 years
- <3.0 cm invasive breast cancer
- Node negative
- Negative surgical margins after breast conserving surgery
- No chemotherapy
- No regional nodal irradiation
- No XRT boost allowed



Brunt et al. JCO 2020; 38(28):3261-3272

UK FAST PRIMARY ENDPOINT

Primary Endpoint:

2-year and 5-year change in photographic appearance relative to post-surgery/pre-XRT appearance

Rated by 2 blinded observers as none, mild, or moderate based on changes in size, shrinkage, and shape

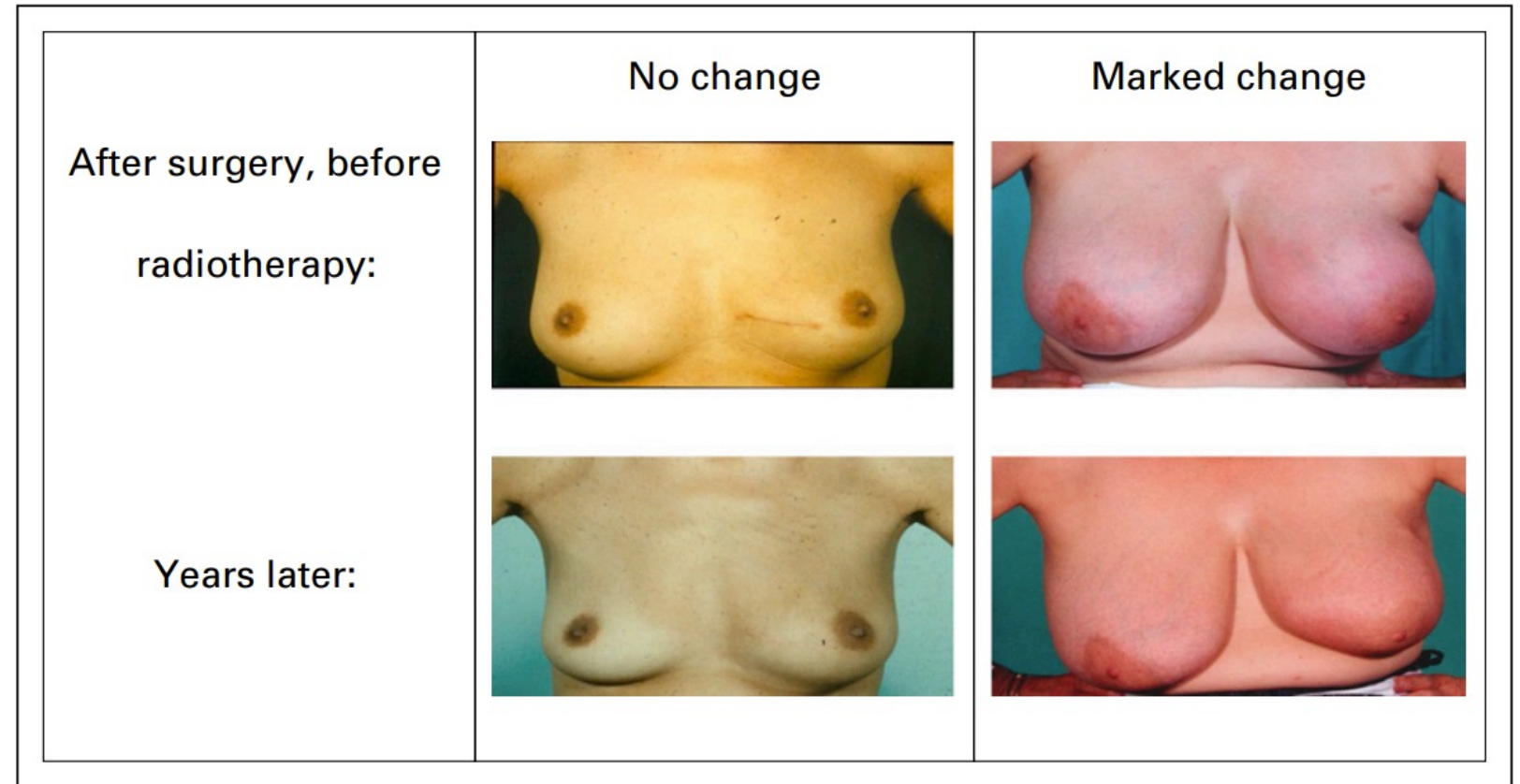


FIG A1. Examples of no change and marked change in photographic breast appearance.

UK FAST PATIENT/TUMOR CHARACTERISTICS

- ~60% of patients \geq 60 years of age
- >75% invasive ductal carcinoma
- 80% of tumors <2.0 cm
- ~90% of tumors Grade 1 or 2
- ~88% of tumors hormone receptor positive
- ~80% of patients with small or medium breast size
- ~73% of patients had a small or medium surgical deficit

The FAST Trialists Group 2011 (100): 93-100

UK FAST CHANGE IN PHOTOGRAPHIC APPEARANCE AT 2 AND 5 YEARS

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, <i>P</i> ^a	Comparison Between 30 Gy and 28.5 Gy, <i>P</i> ^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

Brunt et al. JCO 2020; 38(28):3261-3272

UK FAST ACUTE SKIN REACTIONS

Acute skin reactions during treatment by fractionation schedule.

RTOG grade	Fractionation schedule			Total (%)
	50 Gy (%)	30 Gy (%)	28.5 Gy (%)	
0 = No visible change	8 (7.3)	28 (25.2)	42 (39.6)	78 (23.9)
1 = Faint/dull erythema	51 (46.4)	67 (60.4)	53 (50.0)	171 (52.3)
2 = Tender/bright erythema ± dry desquamation	39 (35.5)	13 (11.7)	9 (8.5)	61 (18.7)
3 = Patchy moist desquamation, moderate oedema	12 (10.9)	3 (2.7)	2 (1.9)	17 (5.2)
4 = Confluent moist desquamation, pitting oedema	0	0	0	0
Total with known RTOG grade for acute skin reaction	110 (100)	111 (100)	106 (100)	327 (100)
Not recorded ^a	187	192	196	575
Not known	5	5	3	13
Total randomised	302	308	305	915

^a Acute toxicity data was not collected from the beginning of the trial.

The FAST Trialists Group 2011 (100): 93-100

UK FAST ACUTE SKIN REACTIONS

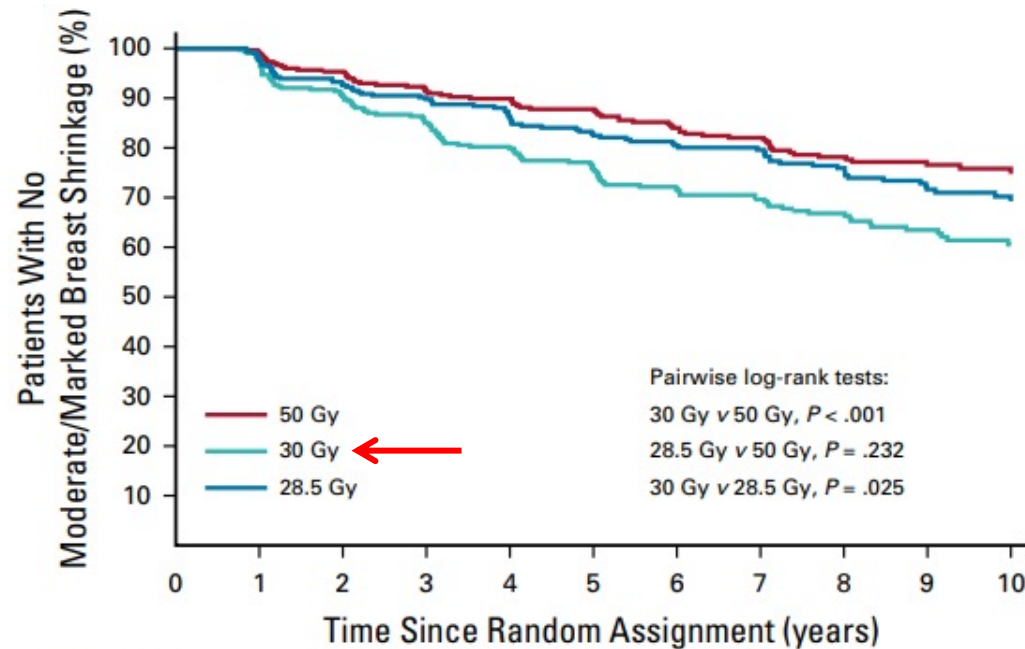
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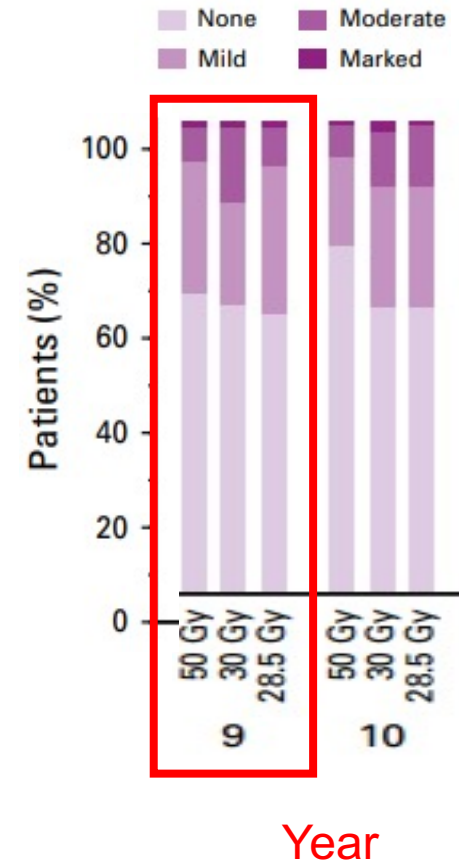
UK FAST

- Median follow-up 9.9 years
- Among all patients, 11 Locoregional recurrences (10-year rate of LRR was 1.3%)
- No differences in LRR between arms



No at risk (events):

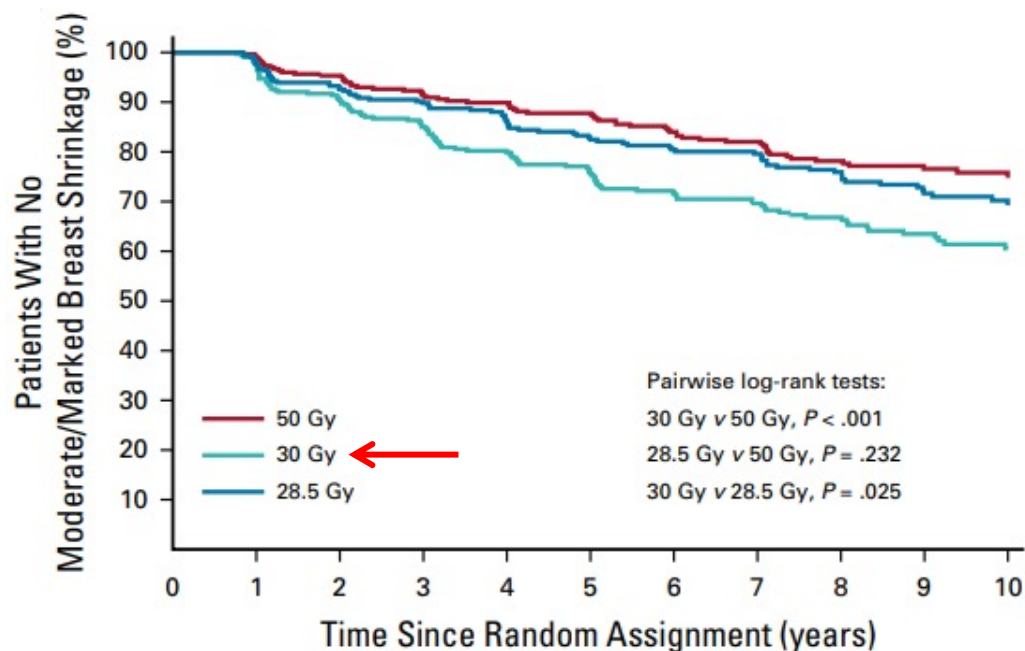
50 Gy	301 (3)	297 (11)	284 (12)	265 (4)	257 (6)	240 (10)	214 (5)	197 (9)	166 (3)	125 (2)	68
30 Gy	304 (7)	295 (22)	271 (16)	249 (15)	231 (12)	202 (10)	175 (5)	157 (6)	133 (6)	98 (4)	63
28.5 Gy	298 (7)	290 (15)	271 (8)	255 (10)	238 (10)	210 (5)	196 (2)	179 (8)	155 (8)	119 (3)	69



Brunt et al. JCO 2020; 38(28):3261-3272

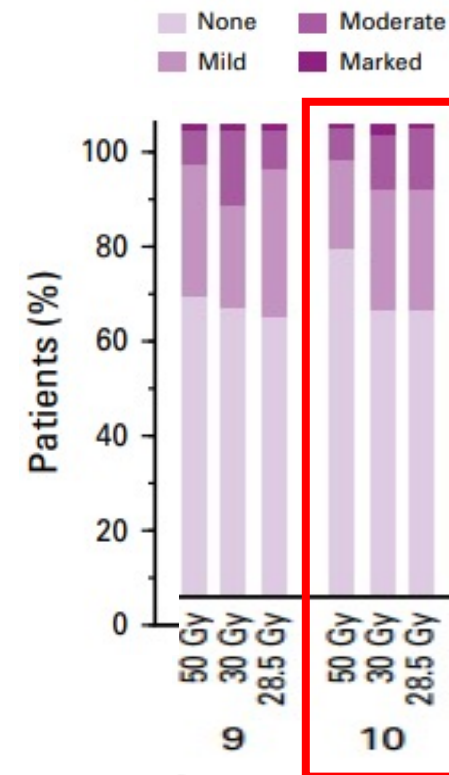
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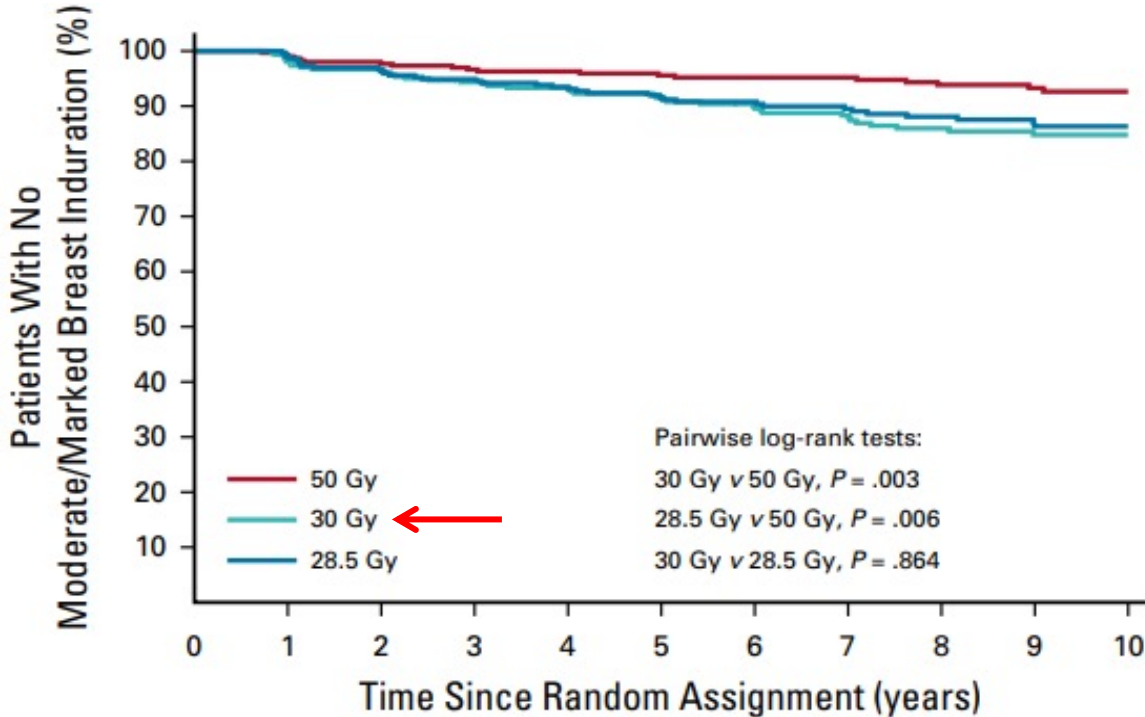
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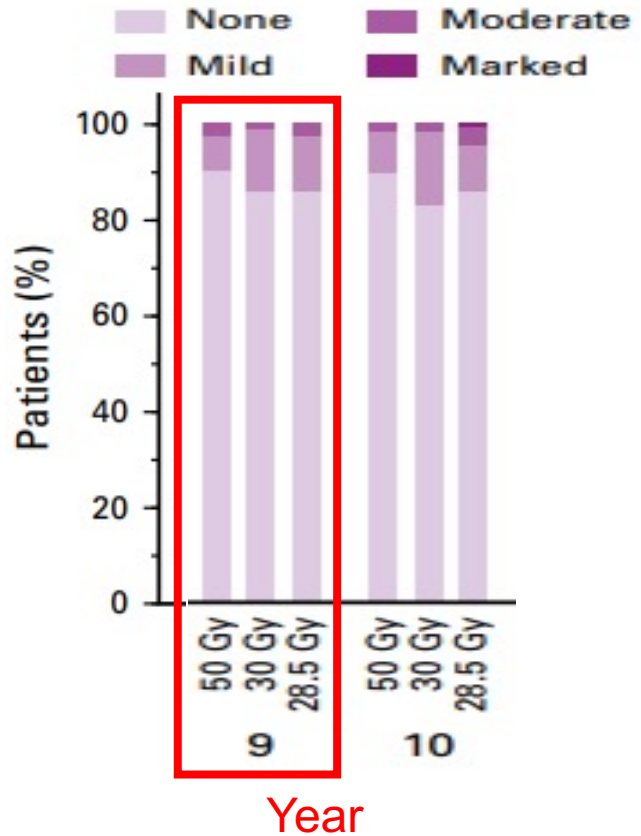
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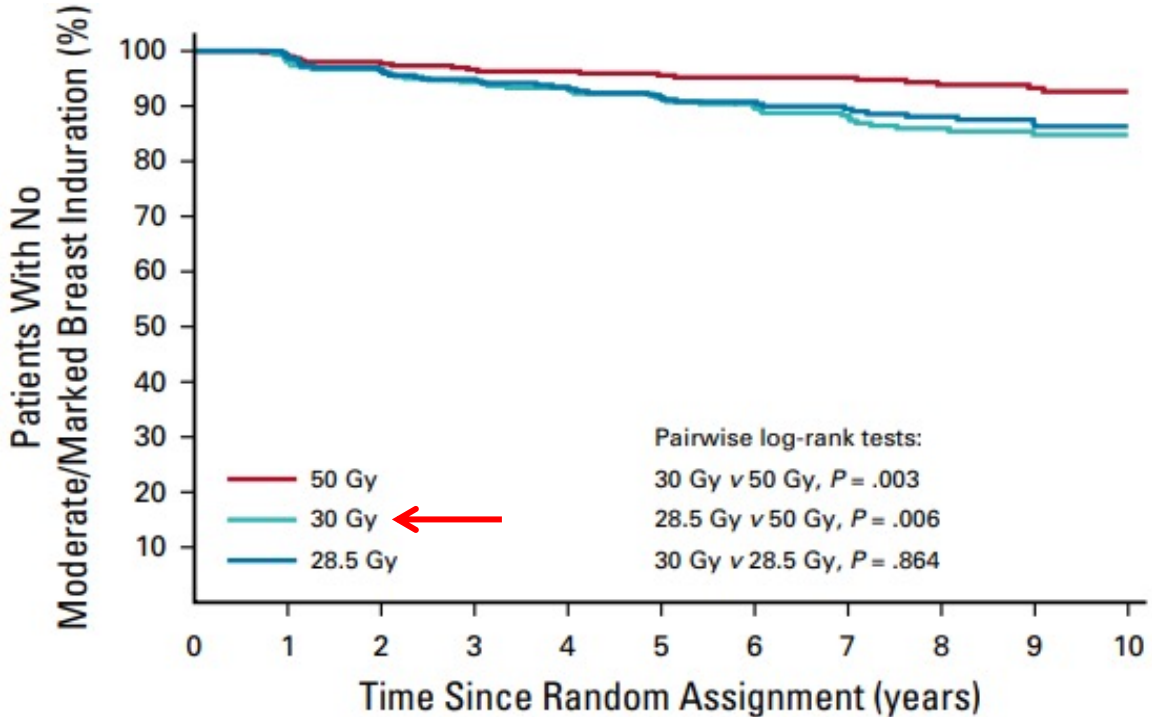
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50 Gy	301 (3)	297 (4)	290 (3)	280 (1)	274 (2)	259 (1)	240 (0)	226 (3)	198 (1)	156 (1)	84
30 Gy	304 (6)	296 (4)	290 (7)	277 (3)	270 (5)	246 (5)	218 (3)	194 (5)	170 (2)	129 (0)	85
28.5 Gy	298 (3)	294 (7)	283 (5)	269 (4)	256 (5)	234 (2)	219 (3)	195 (3)	174 (3)	140 (0)	78



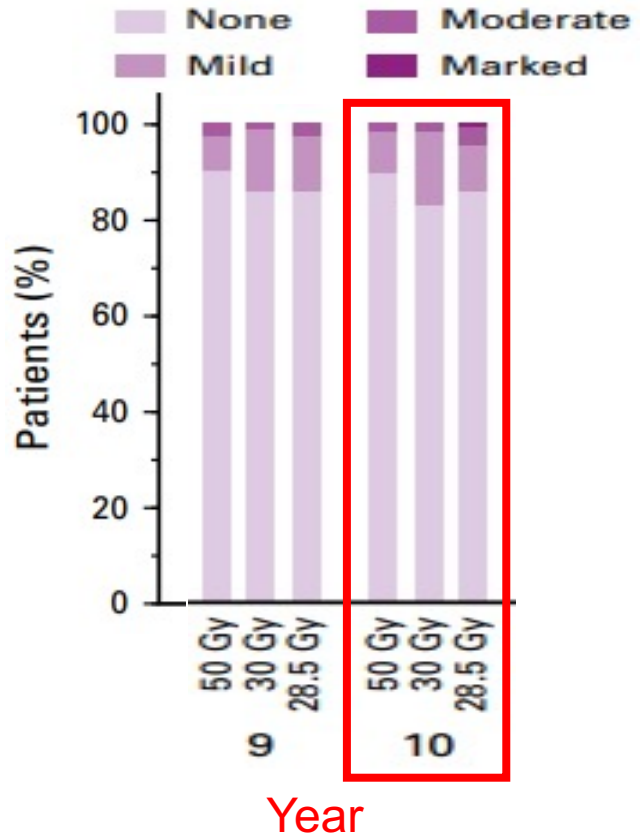
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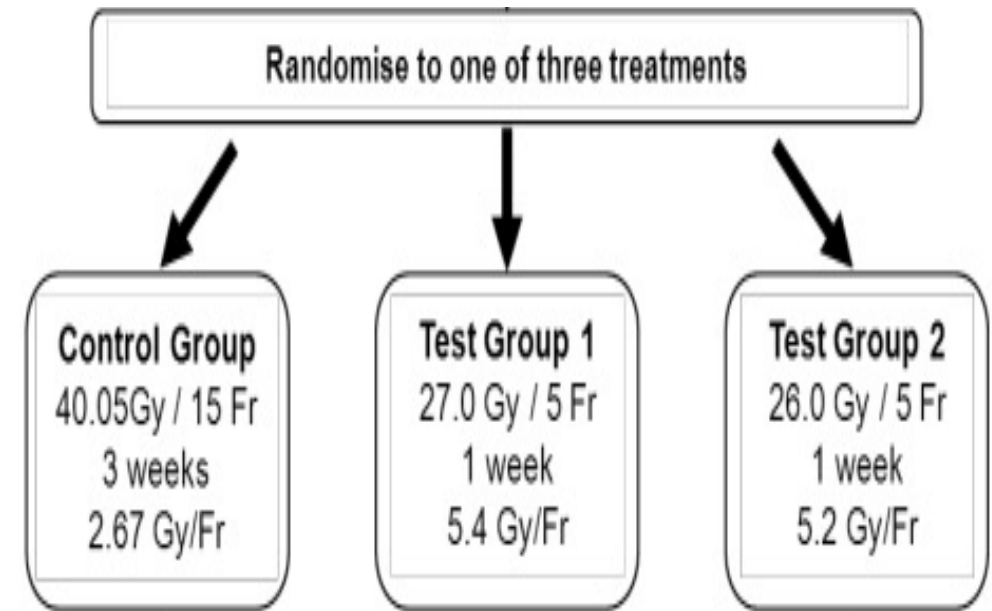
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UK FAST CONCLUSIONS

- 28.5 Gy in 5 fxns given once weekly to the whole breast is a safe and effective option for patients:
 - \geq age of 50 &
 - Grade 1 or 2 hormone receptor positive, node negative tumors <2.0cm in size &
 - Negative surgical margins who are not recommended chemotherapy
- 28.5 Gy in 5 fxns given one time per week and 50 Gy in 25 fxns given daily are regimens associated with similar rates of 5-year change in photographic appearance of the breast and normal tissue toxicities
- At 10 years, there is a signal that 28.5 Gy in 5 fxns given once weekly is associated with increased moderate/marked breast shrinkage and induration

UK FAST-FORWARD

- Phase III Trial of 5 large fractions given daily in one week versus 15 fractions given daily in 3 weeks
- Primary endpoint: Ipsilateral breast tumor relapse
- Age \geq 18 years
- pT1-3, N0-1, M0
- Negative surgical margins after breast conserving surgery or mastectomy (reconstruction allowed)
- Nodal radiotherapy was not allowed in main study (allowed in a substudy)
- Chemotherapy was allowed



Allowed Sequential Boost 10-16 Gy in 2 Gy fxns

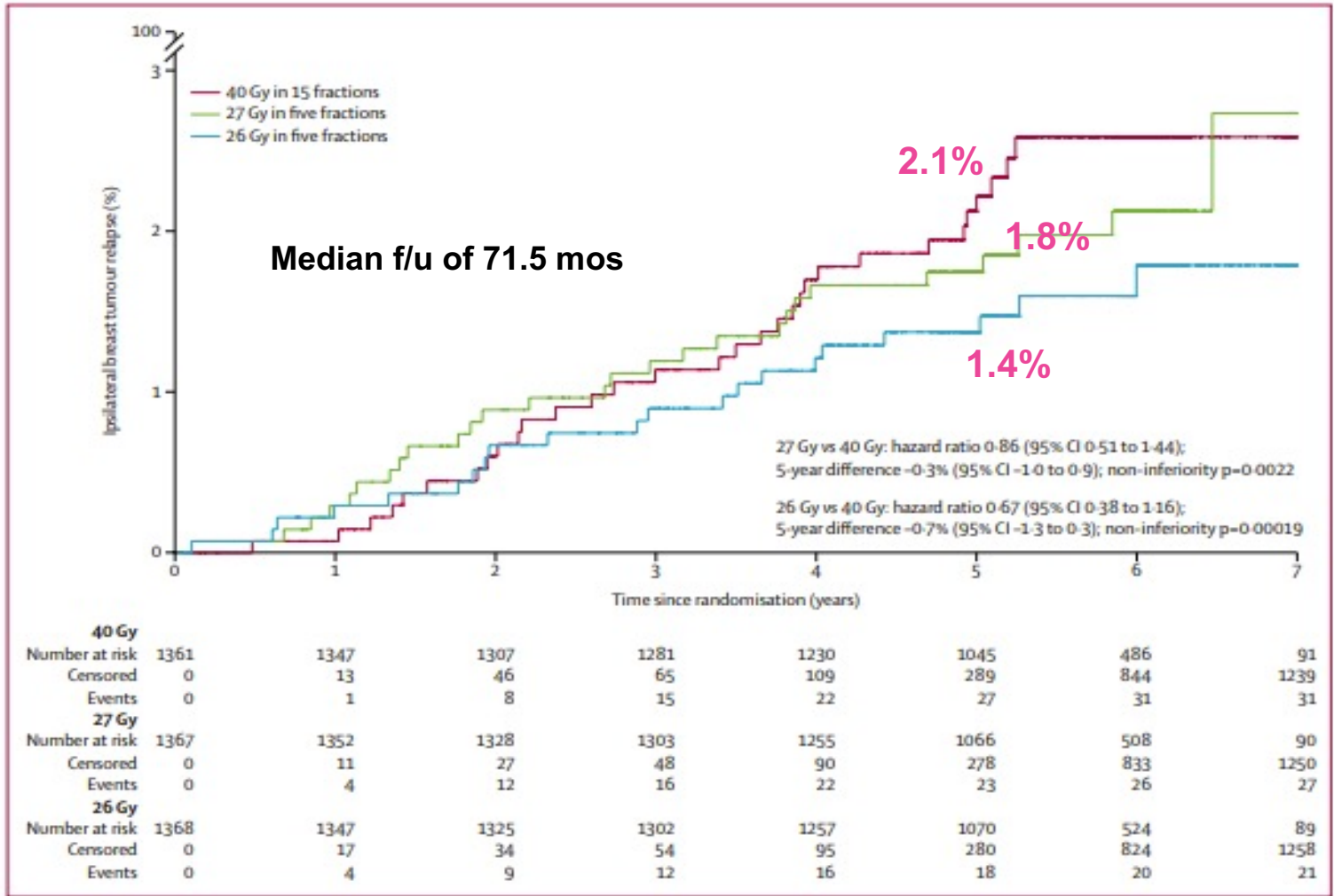
Brunt et al. Lancet 2020; 395: 1613-1626

UK FAST-FORWARD PATIENT/TUMOR CHARACTERISTICS

- >85% of patients \geq 50 years of age
- >80% node negative
- 93% breast conserving surgery
- ~70% of tumors Grade 1 or 2
- ~80% invasive ductal carcinoma
- Median tumor size of 1.6cm
- ~80% tumors hormone receptor positive and Her2 negative
- ~25% received chemotherapy
- ~25% received radiation boost

Brunt et al. Lancet 2020; 395: 1613-1626

UK FAST-FORWARD RESULTS



**5-year IBTR:
26 Gy in 5 fxns WBI
delivered daily over
one week
is non-inferior to
40 Gy in 15 fxns WBI
delivered in 3 weeks**

Brunt et al. Lancet 2020; 395: 1613-1626

FAST-FORWARD TOXICITIES

Acute Toxicities

Late Toxicities at 5-years

Acute skin toxicities reported. Acute toxicity substudy 1 – Worst acute CTCAE score according to treatment.

Worst RTOG grade (on or post RT)	40 Gy/15F N = 44 N (%) ^a	27 Gy/5F N = 51 N (%) ^a	26 Gy/5F N = 52 N (%) ^a
0	0	2 (4)	3 (6)
1	14 (32)	24 (47)	32 (62)
2	24 (55)	20 (39)	14 (27)
3	6 (14)	5 (10)	3 (6)
4	0	0	0
Percentage of RTOG grade 3+ (upper limit of one-sided 95% CI)	13.6 (25.2)%	9.8 (19.5)%	5.8 (14.2)%

^a Percentages calculated from those evaluable.

	40 Gy	27 Gy	26 Gy
Any adverse event in breast/chest wall	10.6%	15.9%	12.2%
Breast distortion	4%	6.1%	5%
Breast shrinkage	5.5%	8.2%	6.8%
Breast induration (outside tumor bed)	0.8%	2.3%	1.6%
Telangiectasia	1%	1.6%	1.6%
Breast or chest wall edema	1.5%	3.4%	2.4%
Breast or chest wall discomfort	3.8%	4.3%	4%

More acute toxicities in 40 Gy arm and 27 Gy arms than 26 Gy arm

Brunt et al. Radiotherapy and Oncology 2016; 120:114-118.
Brunt et al. Lancet 2020; 395: 1613-1626

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**More late toxicities in 27 Gy arm than 40 Gy arm
26 Gy arm at least comparable if not better than 40 Gy arm but potential
increased induration in 26 Gy arm developing long-term**

Brunt et al. Radiotherapy and Oncology 2016; 120:114-118.
Brunt et al. Lancet 2020; 395: 1613-1626

FAST-FORWARD CONCLUSIONS

- 5-year data indicates 26 Gy in 5 daily fractions given over one week to the whole breast is effective and safe for patients \geq age 50 with Grade 1 or 2 hormone receptor positive, node negative tumors <2.0 cm in size, and negative surgical margins
- Given the UK FAST data indicating more changes to the breast at 10 years, long-term follow-up data from FAST-FORWARD will provide valuable information on changes to the breast
- Data on 5 daily treatments to patients requiring regional nodal radiation is forthcoming

EQUIVALENT DOSE

- As dose per fraction increases, the total dose required to achieve tumor cell kill decreases
- EQD_{2Gy} : equivalent dose needed in 2 Gy/fxn to achieve the same effective dose as a hypofractionated treatment with smaller total dose delivered in larger fraction sizes

$$EQD2 = \frac{BED}{\left(1 + \frac{2}{\alpha/\beta}\right)}$$

EQD₂ HYPOFRACTIONATION VERSUS ULTRASHORT WBI






Table 3 Overview of different fractionation regimens used in clinical trials

Regimen	Treatment schedule over the course of 5 weeks	EQD _{2Gy} ($\alpha/\beta = 3.5$)
Conventional 25 × 2 Gy		50 Gy
START A 13 × 3.0/3.2 Gy [6]		46.1 Gy/50.4 Gy
START B 15 × 2.67 Gy [7]		44.9 Gy
→ FAST 5 × 5.7/6.0 Gy [27] 28.5 / 30 Gy		47.7 Gy/51.8 Gy
→ FAST-Forward 5 × 5.2/5.4 Gy [26] 26 / 27 Gy		41.1 Gy/43.7 Gy

EQD_{2Gy} Dose equivalent delivered in 2 Gy-fractions without time loss-factor.

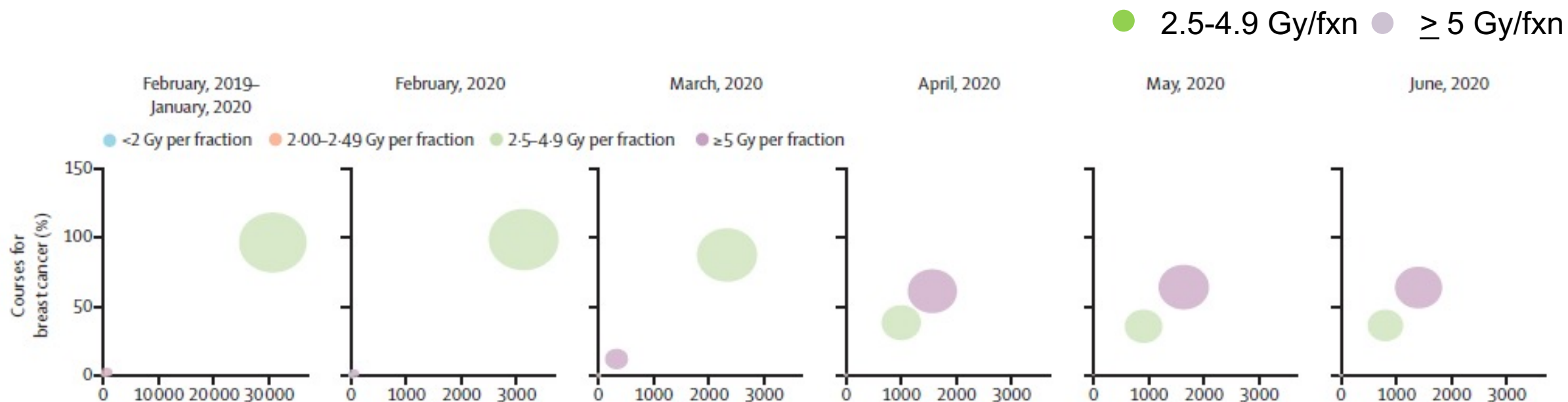
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EQD_{2Gy} Dose equivalent delivered in 2 Gy-fractions without time loss-factor.

ADOPTION OF ULTRASHORT HYPOFRACTIONATION



Use increased from 0.2% in April 2019 to 60.6% in April 2020 in the United Kingdom due to COVID pandemic

Spencer et al *Lancet Oncol* (2021);22:309-320

CONCLUSIONS

- As systemic treatments have become more effective and our understanding of tumor biology improves, there is a clear trend in breast radiation oncology to decrease the dose, the number of days of treatment, and the target volumes
- For patients \geq age 50 with T1N0, hormone receptor positive invasive ductal carcinoma treated with breast conserving surgery and negative margins, 28.5 Gy in 5 fractions given once a week is a viable option
- With survival expected to be longer than 10 years in most patients with early-stage breast cancer, it is important to counsel patients on potential long-term side effects of ultrashort whole breast irradiation (i.e., 5 large doses) including breast shrinkage and induration, particularly in women with large breasts and large surgical deficits

Thank you