Breast cancer: Hypofractionation

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Fractionation in Breast Cancer

Standard radiation (WBI)	(6 -6.5 weeks)
Hypofractionation (WBI)	(3 - 4 weeks)
Hypofractionation (WBI)	(once / wk for 5 wks)
Accelerated Partial breast RT	(1 week)
Intra-operative RT	(1 day)

The future, according to some scientists, will be exactly like the past, only far more expensive.

John Sladek, American Science Fiction author, 1937-2000.

Hypofractionation: Benefits

1. Convenience
2. Cost
3. Shorter wait times (quick turnaround)
4. ? More effective
5. ? Lower toxicity

Hypofractionation: a brief history and concerns

-1960s, MDACC: 3 and 5 day/week treatments for breast cancer → similar acute toxicities, significantly worse late toxicities with hypofractionation

-Other studies from 1960s-80s also showed increased late toxicities with hypofractionation (used nominal standard dose model – total dose was not reduced)

lmost all publications, a high percentage of severe complications after hypofractionation have been reported. There is overwhelming evidence tha
raction size of more than 2 Gy produces late unfavorable sequelae, and therefore, despite the inconvenience for patients and the taxing of machi
me, hypofractionation should not be used unless there is a specific rationale concerning the tumor characteristics of doing so. In that case the t

(Fletcher Radiother Oncol, 1991)

Estimates of α/β value for breast cancer- Start trials(n = 3646)

Cox proportional hazards regression model:

Total dose, dose per fraction, local-regional relapse data

- Late adverse effects (815 events) -

  $\alpha/\beta = 3.1$Gy (95% CI = 2 - 4.2)

- Tumour relapse (349 events) -

  $\alpha/\beta = 3.5$Gy (95%CI = 1.2 – 5.7)

Haviland et al , Lancet p1086–1094, October 2013

Randomized Trials: HF vs CF

reatment and patient characteristics

	Ontario	START Pilot	START A	START B
ountry	Canada	UK	UK	UK
ime of accrual	1993–1996	1986–1998	1998–2002	1999–2001
atients, n	1234	1410	2236	2215
lastectomy	0%	0%	15%	8%
tandard-RT	50 Gy/25 fx in 5 we.	50 Gy/25 fx in 5 we.	50 Gy/25 fx in 5 we.	50 Gy/25 fx in 5 we
ypofract. RT (1)	42.5 Gy/16 fx in 3.1 we.	39 Gy/13 fx in 5 we.	39 Gy/13 fx in 5 we.	40 Gy/15 fx in 3 we
ypofract. RT (2)	–	42.9 Gy/13 fx in 5 we.	41.6 Gy/13 fx in 5 we.	–
oost-RT	0%	74.5% (14 Gy/7 fx)	60.6% (10 Gy/5 fx)	42.6% (10 Gy/5 fx)
egional-RT	0%	20.6%	14.2%	7.3%
lean age	50–59 years	54.5 years	57.2 years	57.4 years
N positive	0%	32.7%	28.8%	22.8%
umor size >=T2	20.0%	42.5%	48.6%	35.9%
djuvant CHX	11.0%	13.9%	35.5%	22.2%

anadian Trial (1993-1996)

1,234 women with pT1-3 breast cancer s/p lumpectomy w ALND (I and II)

Hypofractionation and acceleration

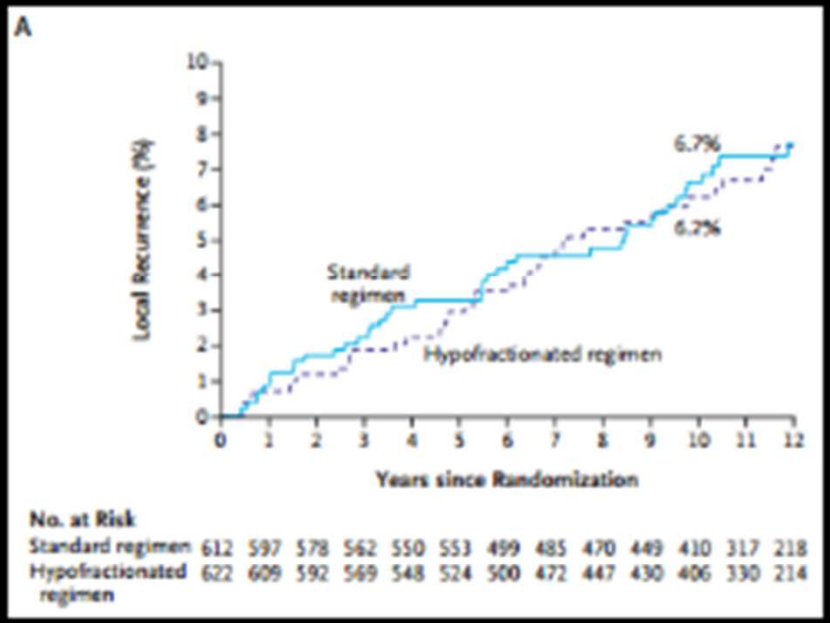
50Gy in 25 fx
2Gy/fx (35 days)

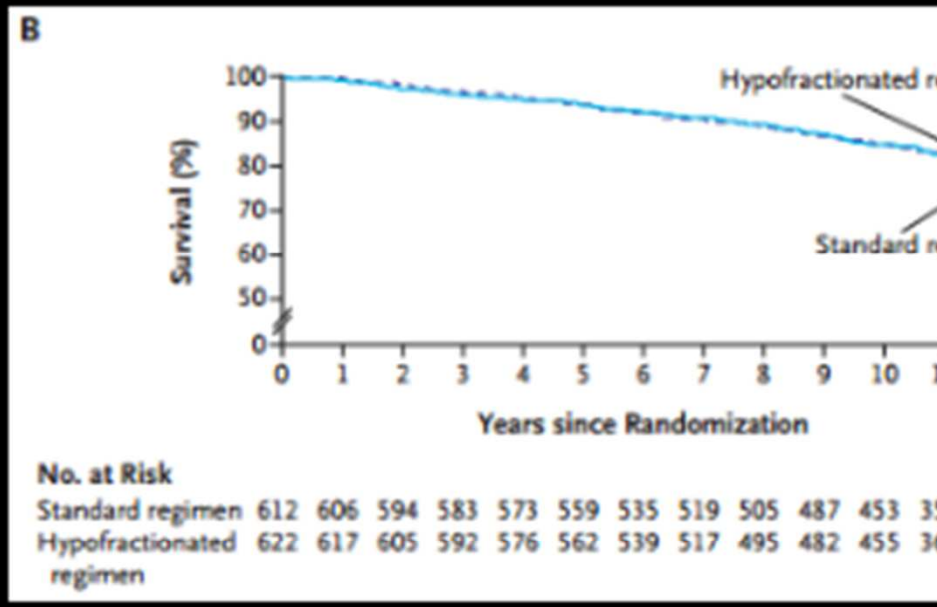
42.5Gy in 16 fx
2.65 Gy/fx (22 days)

- boost
- paration ≤ 25cm
- ratified by age, size, use of adjuvant systemic
- rapy

(Whelan et al NEJM 2010)

anadian Trial





- ledian f/u 12 years
- 0-year LR: 6.7 (50Gy) vs. 6.2% (42.5Gy); non-inferiority (p<0.001)
- -year OS : 84.4% (50Gy) vs. 84.6% (42.5Gy)
- -year "excellent/good" cosmetic outcome: 71.3% (50Gy) vs. 69.8% (42.5

START-A

2,236 women with pT1-3, N0-1 breast cancer s/p lumpectomy (85%) or MRM (15%)

All regimens lasted 5 weeks for un-confounded test of sensitivity to fraction
ze

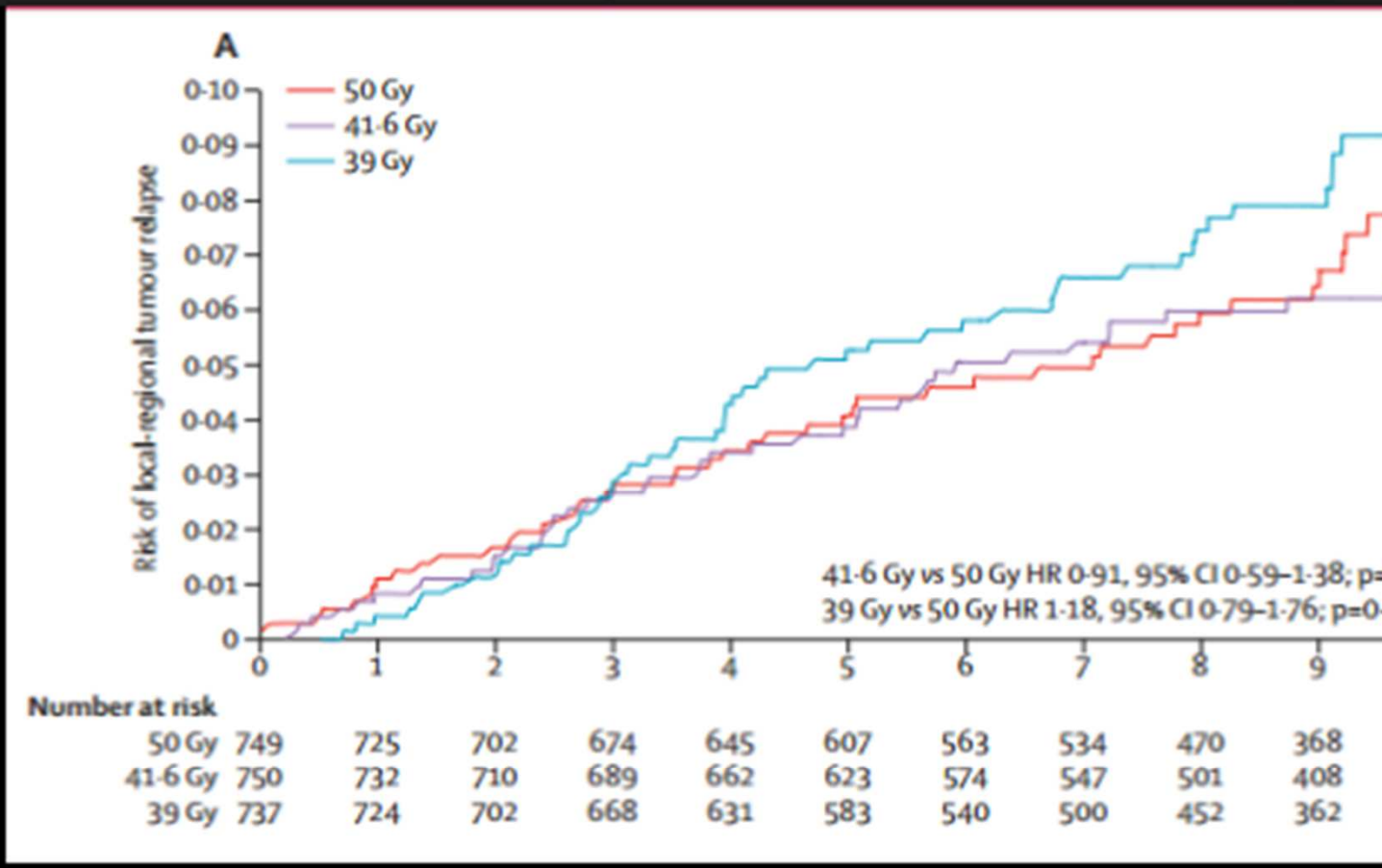
Boost (10Gy) allowed*

(Haviland et al Lancet 2013)

START-A

α/β ratio

LR relapse → 4 Gy
Shrinkage → 3.5 Gy
Induration → 4 Gy
Edema → 4.7 Gy
Telangectasia →3.8 Gy



Conclusion: breast cancer is as sensitive to fraction size as normal tissues

ART-B (1999 to 2001)

2,215 women with pT1-3,N0-1 breast cancer s/p lumpectomy or MRM

Hypofractionated and accelerated Rx

50Gy/25fx
2Gy fractions over 5 weeks)

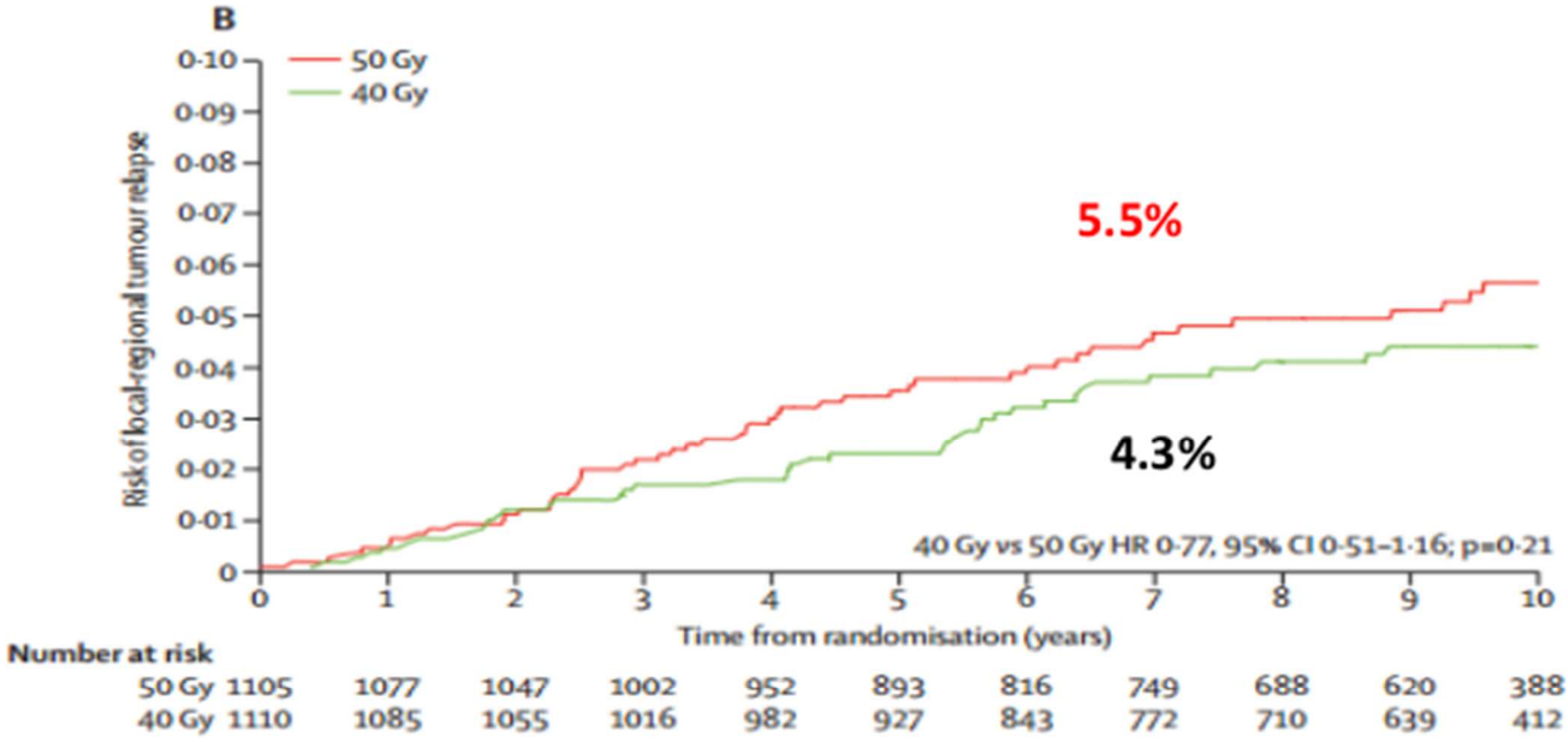
40Gy/15 fx
(2.67Gy fractions over 3 weeks)

Boost (10Gy) allowed*

Inclusion:
- pT1-3a
-pN0-1 M0
-Clear margins (≥1mm)
-BCS/mastectomy;
- non-immediate reconstruct
-23 sites in the UK;

START-B Trial

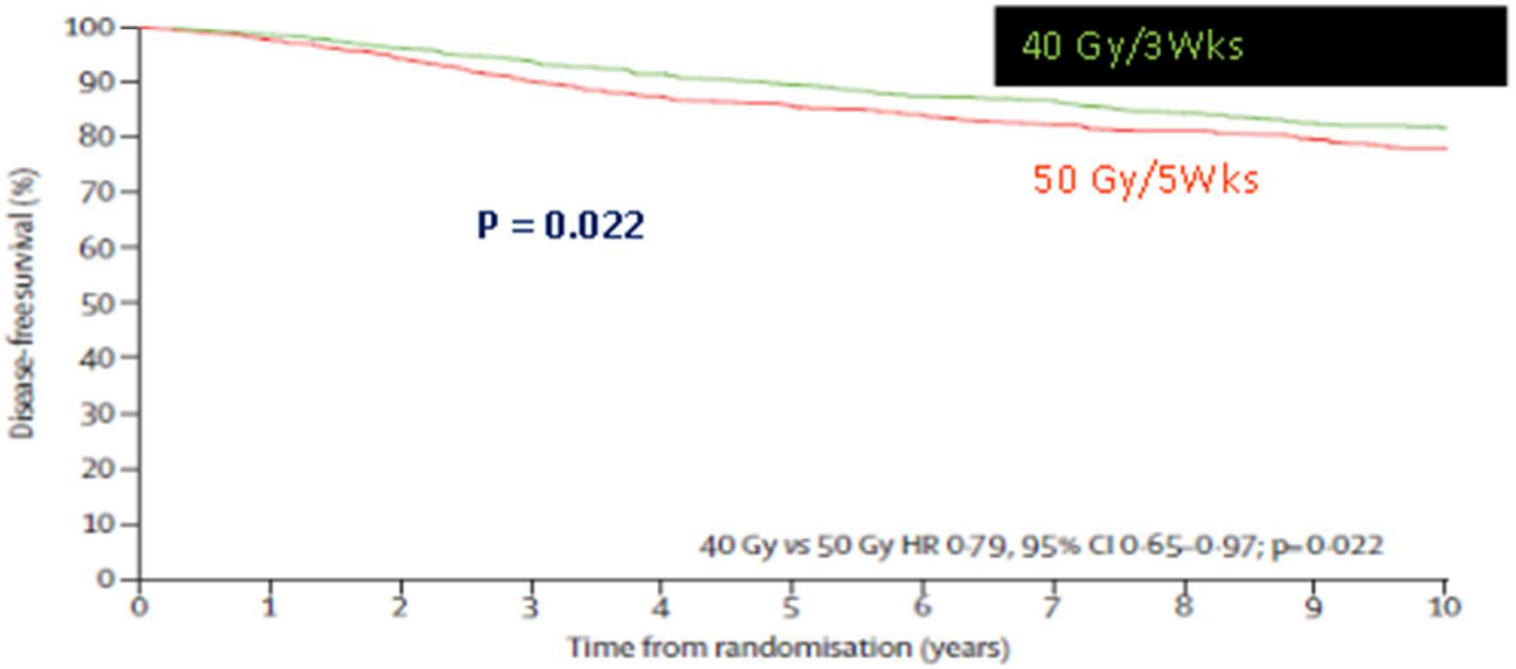
Local Relapse



START trialist group The Lancet 2008; Lancet Onc

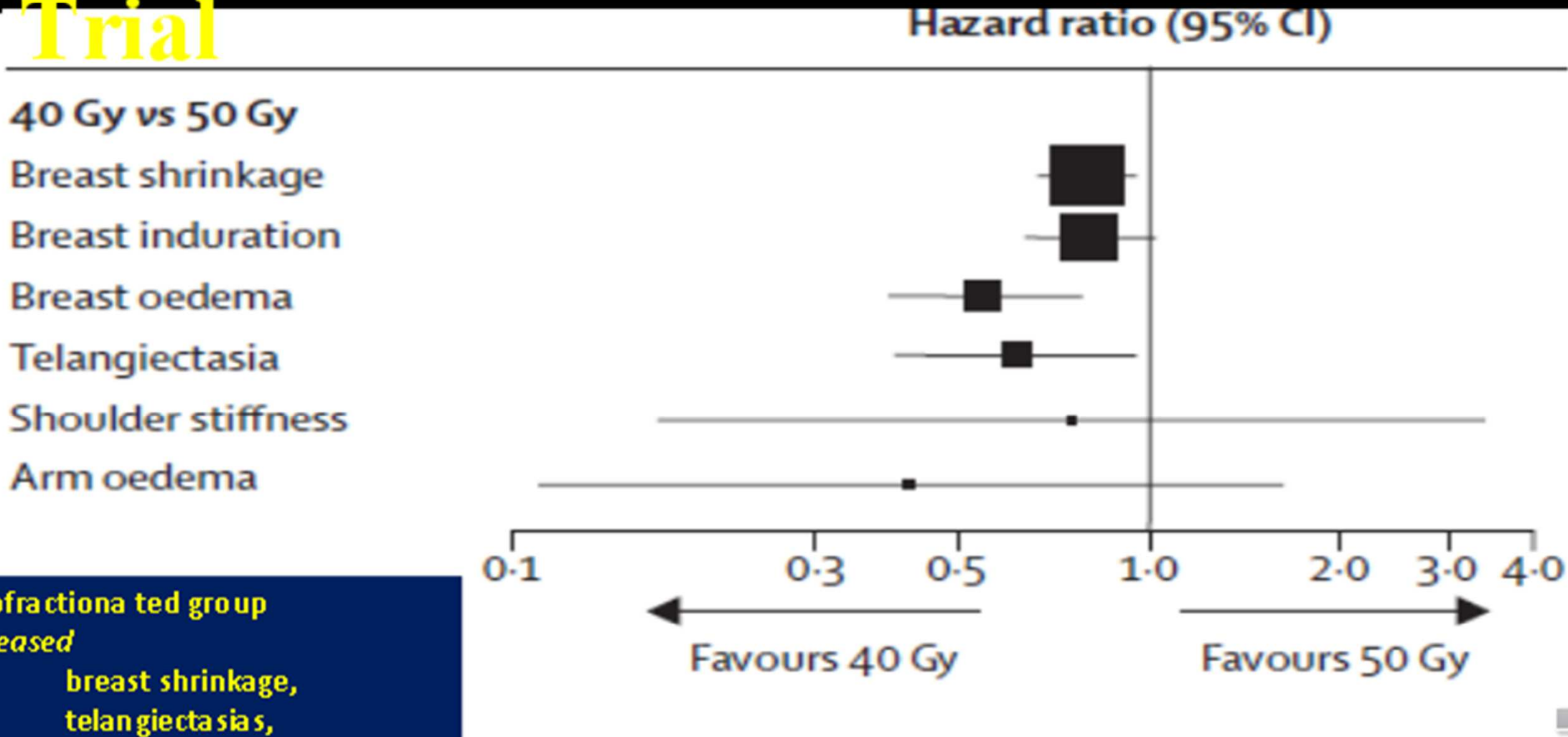
START-B Trial

Disease free survival



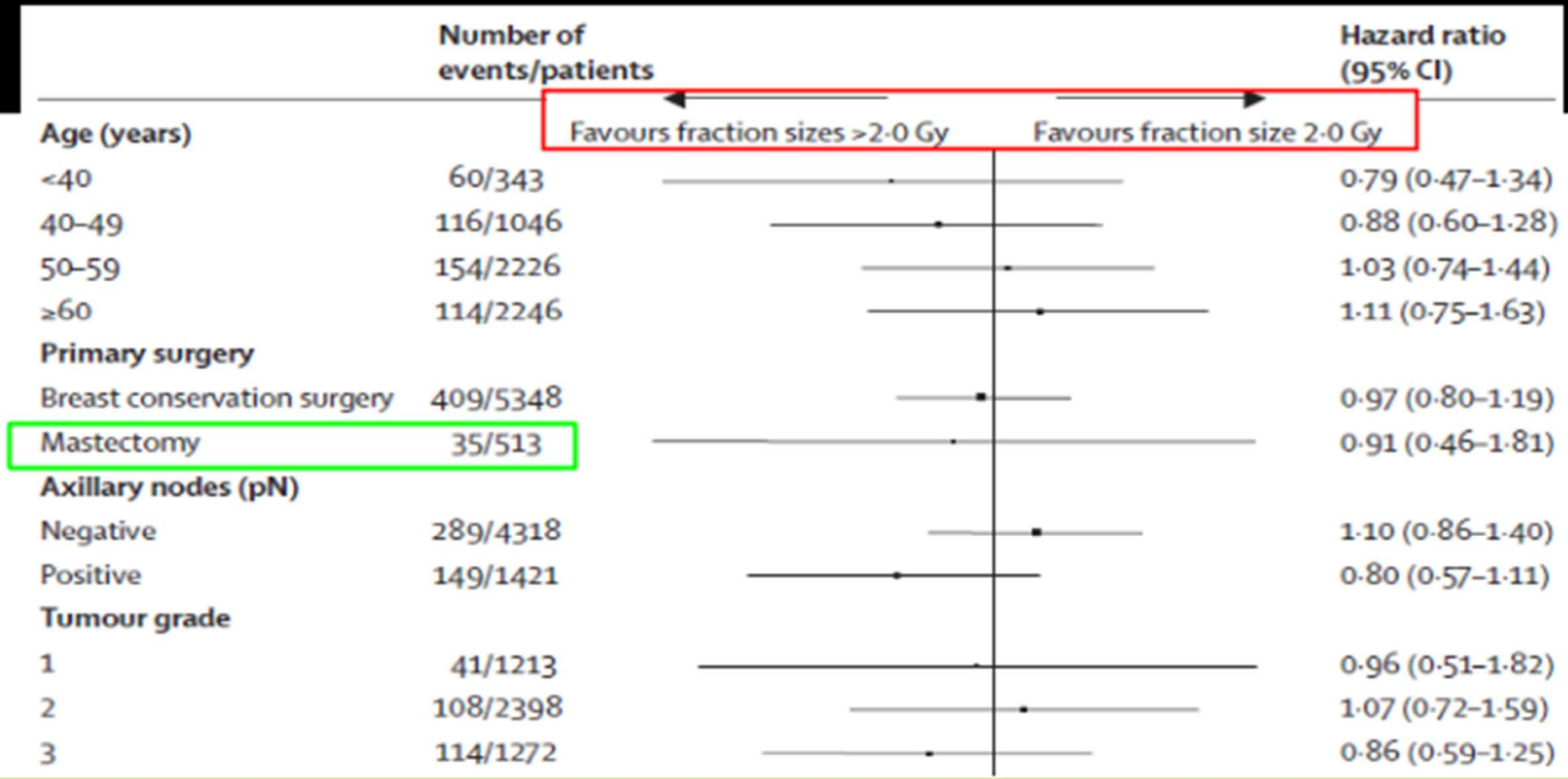
START-B Trial

Cosmetic outcome



ypofractiona ted group
ecreased
breast shrinkage,
telan giectasias,
breast edema (HR=0.77)

atients eligible for hypofractionation



onclusion: 40Gy /15 fractions is equivalent in efficacy and
oxicity to 50Gy /25 fractions

le 3 Randomized Trials Evaluating Hypofractionated vs Conventional Whole Breast Irradiation—ient Subgroup Clinicopathologic and Treatment Characteristics

ent/Treatment ors	RMH/GOC [5,6] (N = 1,410)	Canadian [3,4] (N = 1,234)	START A [7,9] (N = 2,236)	START B [8,9] (N = 2,215)
imetric parameters	CADH −5% to +7%	CADH −7% to +7% Separation ≤ 25 cm	CADH ± 5%	CADH ± 5%
< 50 yr	30% (n = 423)	25% (n = 305)	23% (n = 509)	21% (n = 457)
de 3 tumors	NR	19% (n = 233)	28% (n = 629)	23% (n = 509)
tive lymph nodes	33% (n = 274)	0% (excluded)	29% (n = 643)	23% (n = 504)
of chemotherapy	14% (n = 196)	11% (n = 136)	35% (n = 793)	22% (n = 491)
ional nodal irradiation[a]	21% (n = 290)	0%	14% (n = 318)	7% (n = 161)
or bed boost irradiation[b]	75% (n = 1,051)	0%	61% (n = 1,152)	43% (n = 868)
mastectomy irradiation	0%	0%	15% (n = 336)	8% (n = 177)

ents received regional nodal irradiation to the supraclavicular region with same dose and fractionation schedule as the treated breast (except in START A, in two patients in the 41.6-Gy arm received a 39-Gy fractionation scheme for regional nodal treatment).

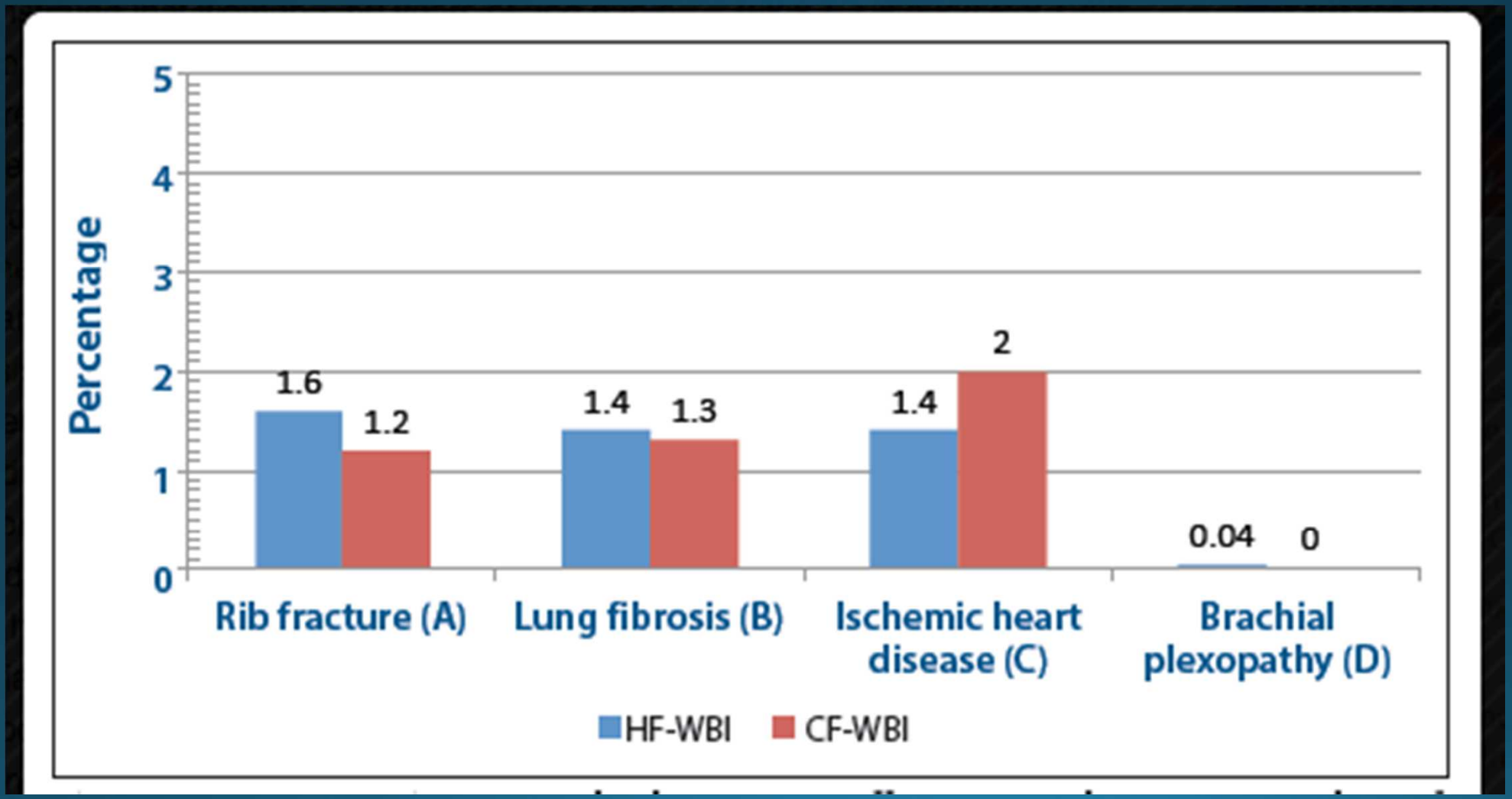
or bed boost scheme was 2 Gy per fx. RMH/GOC boost was 14-Gy boost in 7 fxs. START trial boost after BCS was 10 Gy in 5 fxs.

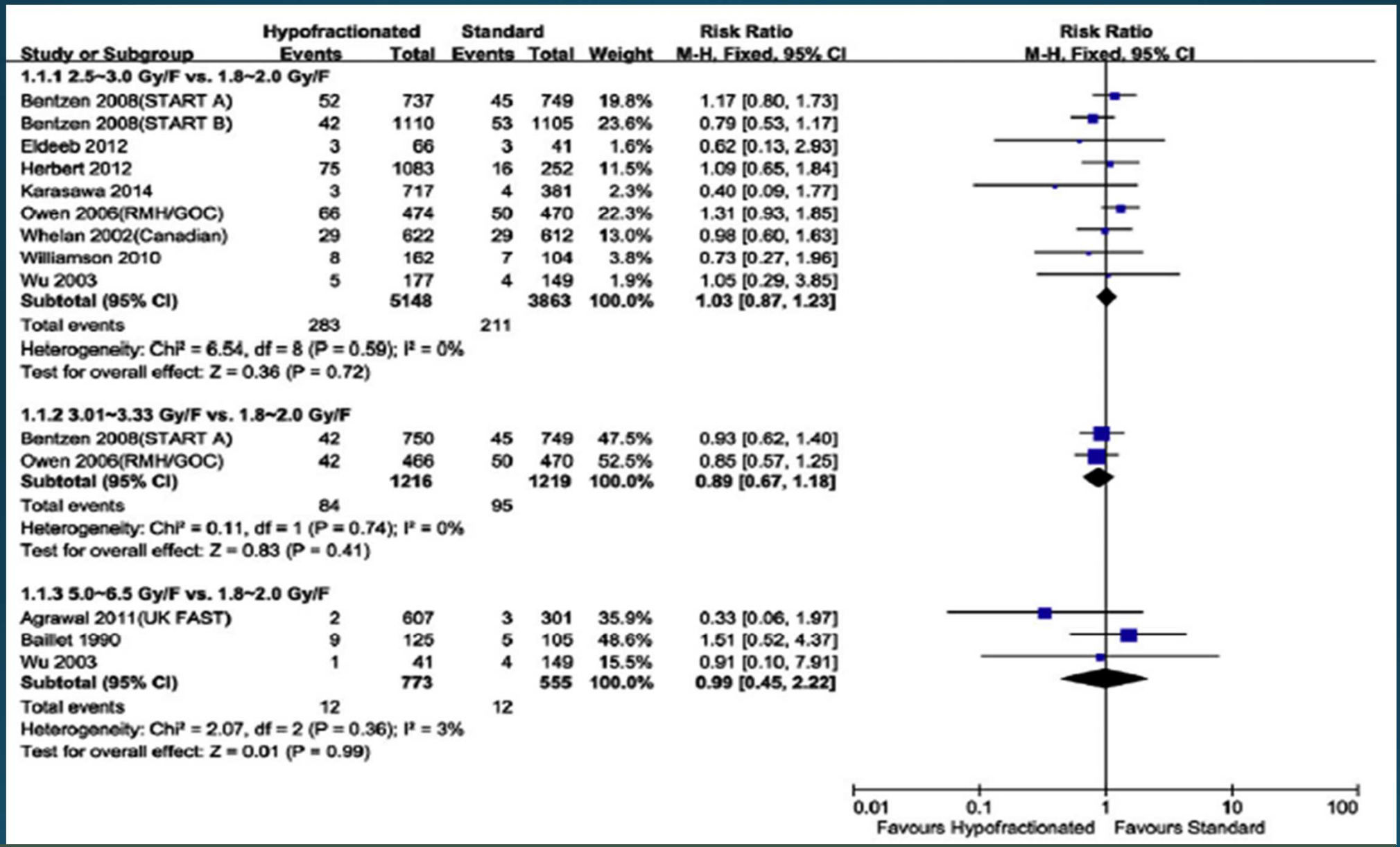
= Breast-conserving surgery; CADH = central axis dose homogeneity; fx(s) = fraction(s); RMH/GOC = Royal Marsden Hospital/Gloucester Oncology Center; ndardisation of Breast Radiotherapy trial.

Table 1 Randomized Trials Evaluating Hypofractionated vs Conventional Whole-Breast Irradiation — Efficacy Outcomes

Trial	Fractionation Scheme[a]	Number of Patients	Stage	Median Follow-up	LRR[b]	OS[c]
RMH/GOC [5,6]	50/25/2.0 (35)	470	T1-3	9.7 yr	12%	NR
1986–1998	42.9/13/3.3 (35)	466	N0-1		10%	
	39/13/3.0 (35)	474			15%	
Canadian [3,4]	50/25/2.0 (35)	612	pT1-2	12 yr	8%	84%
1993–1996	42.5/16/2.66 (22)	622	pN0		7%	85%
START A [7,9]	50/25/2.0 (35)	749	pT1-3a	9.3 yr	7%	80%
1998–2002	41.6/13/3.2 (35)	750	pN0-1		6%	82%
	39/13/3.0 (35)	737			9%	80%
START B [8,9]	50/25/2.0 (35)	1105	pT1-3a	9.9 yr	6%	81%
1999–2001	40/15/2.67 (21)	1110	pN0-1		4%	84%

HF vs CF -Late effects





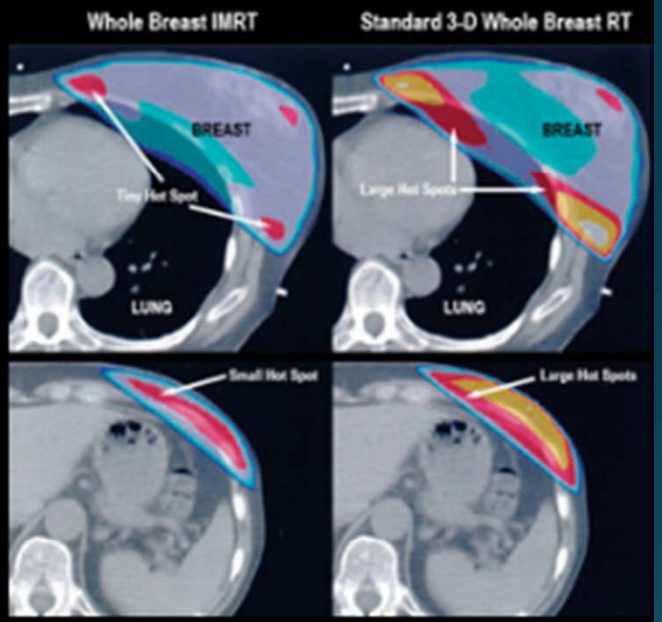
Conclusion- **HFRT With 2.5-3.0 Gy /# should be the better choice for EBC.**

Hypofractionated RT with simultaneous integrated tumor bed boost

HF with SIB

Freedman et al (2012) → 4 weeks

-Phase II study
-75 patients treated from 12/2003 – 11/2005
-Tis-T2, Stage 0-II status post lumpectomy
-Treatment: 45Gy/2.25Gy fractions to whole breast and dose painting to 56Gy/2.8Gy fractions to tumor bed. Total = 20 treatments over 4 weeks with IMRT



-Median follow-up 69 months
-5-year LR: 2.7% (3 patients)
-2 deaths from breast cancer
-Patient-reported cosmesis, pain and arm function and physician-reported cosmesis showed no significant changes within 5 year

HF with SIB

Chadha et al (2012) → 3 weeks

-Phase II study
-160 patients with Tis-T2, N0 breast status post lumpectomy
-Treatment: 40.5Gy/2.7Gy fractions to whole breast and 4.5Gy/3Gy fractions to tumor bed.
Total = 15 treatments over *3 weeks* with 3D planning

-Median f/u 3.5 years
-5-year OS 90%, disease-free survival 97%
-5-year local relapse-free survival 99%
-Toxicities: acute Grade 1 and 2 skin toxicities: 70% and 5%, no late toxicity > Grade 2

TOG 1005…in progress

IMRT or 3D planning allowed

2,354 women accrued

stage I,II with at least one of the
ollowing:
LN+
LVI+
Close margins
ER/PR negative
Grade III
Oncotype >25

DCIS grade III <50 years old

Y p stage 0, I, II resected by
umpectomy after neoadj CT

40.5Gy/2.7Gy fx to whole breast
concomitant 4.5Gy/3Gy fx to tumor bed.
Total = 15 fx / *3 weeks* with 3D planning

Hypofractionated: whole breast RT + concurrent boost (3 weeks total)

Standard: whole breast RT (3-5 weeks) + sequential boost (1-1.5 week) = 6 weeks total

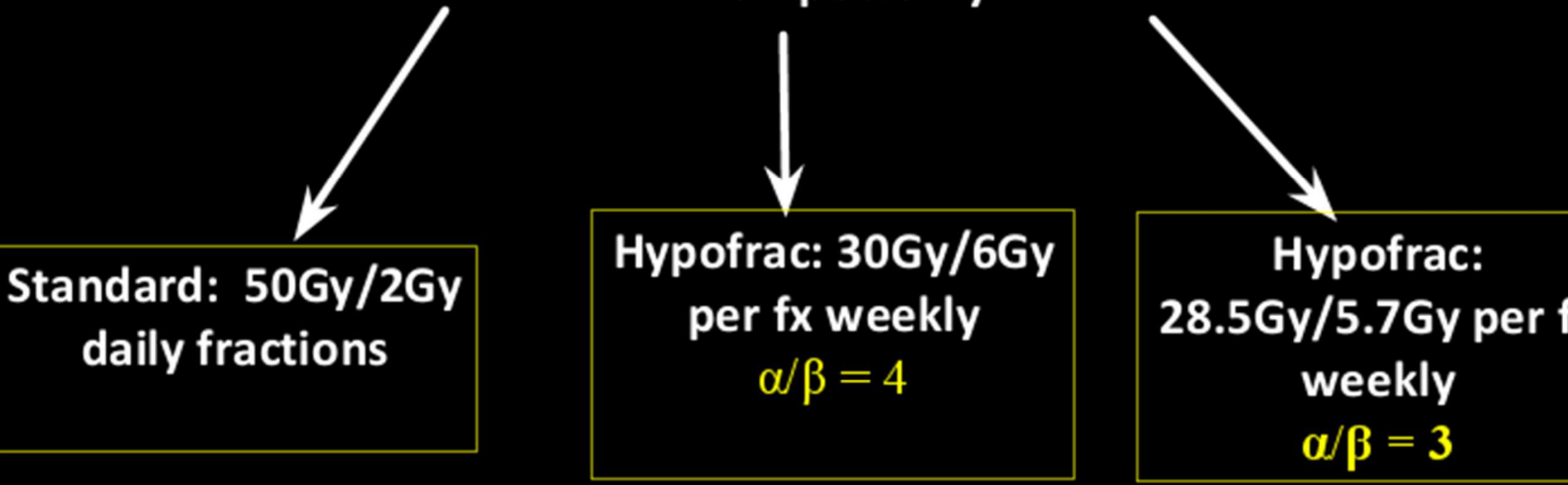
Extreme Hypofractionated RT

UK FAST Trial

(Yarnold et al Radio Oncol 2011)

First results of the randomised UK FAST Trial of radiotherapy hypofractionati
for treatment of early breast cancer (CRUKE/04/015)

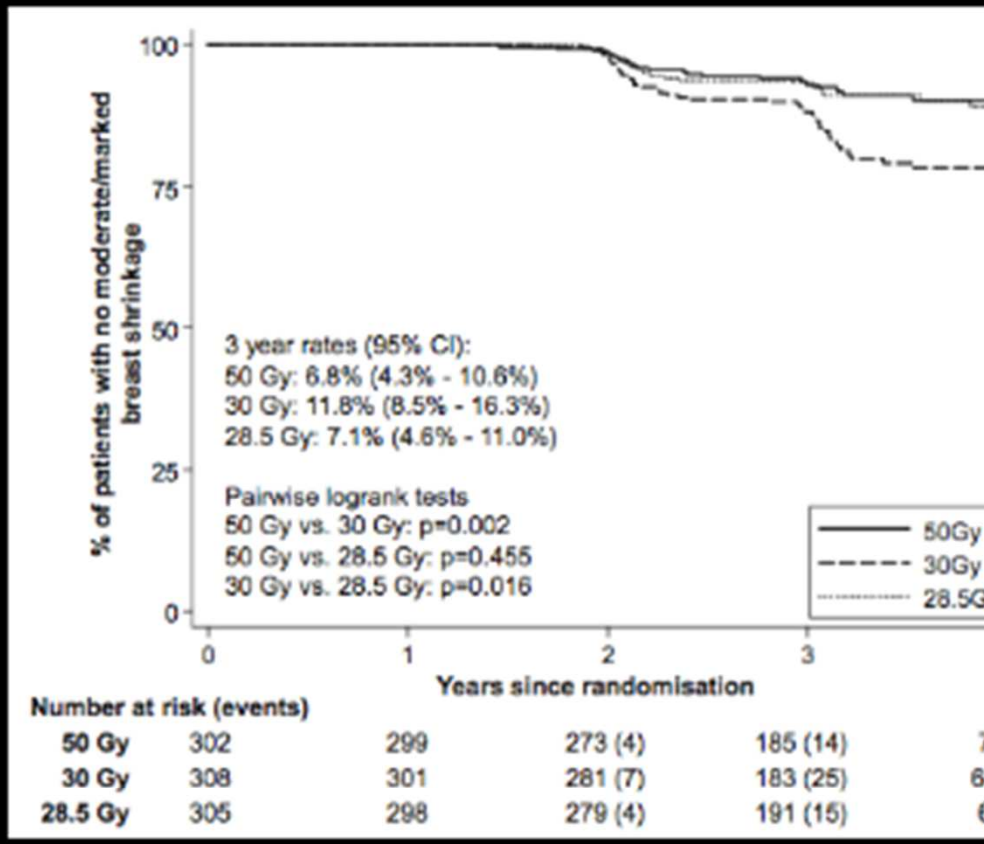
915 women with node negative, ≤3 cm breast cancer s/p lumpectomy



Primary endpoint: 2-year change in photographic breast appearance

First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015)

- Median f/u 3 years
- Mild or marked change per photographic assessment:
  - RR 1.70 (30Gy vs. 50Gy, p<0.0001),
  - RR 1.15 (28.5Gy vs. 50Gy, p=0.489)
- Physician assessed moderate/marked adverse effects:
  - 17.3% for 30Gy,
  - 11.1% for 28.5Gy,
  - 9.5% for 50Gy



UK _ FAST Trial

Median f/u → 3 years

2 local tumor relapses, 23 total deaths

Not powered to test local tumor control differences

Conclusion: 28.5Gy in 5 fr. is comparable to 50Gy in 25 fr. in terms of adverse effects on the breast and both are milder than 30Gy in 5 fractions

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 59–68, 2011

0360-3016/$–see front matter

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doi:10.1016/j.ijrobp.2010.04.042

CLINICAL INVESTIGATION **Breast**

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

BENJAMIN D. SMITH, M.D.,* SOREN M. BENTZEN, PH.D., D.SC.,† CANDACE R. CORREA, M.D.,‡

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria*

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

Table 4 Criteria for Treatment With Hypofractionated Breast Radiation, Based on ASTRO 2011 Consensus Guidelines and Update of the START Trials[23]

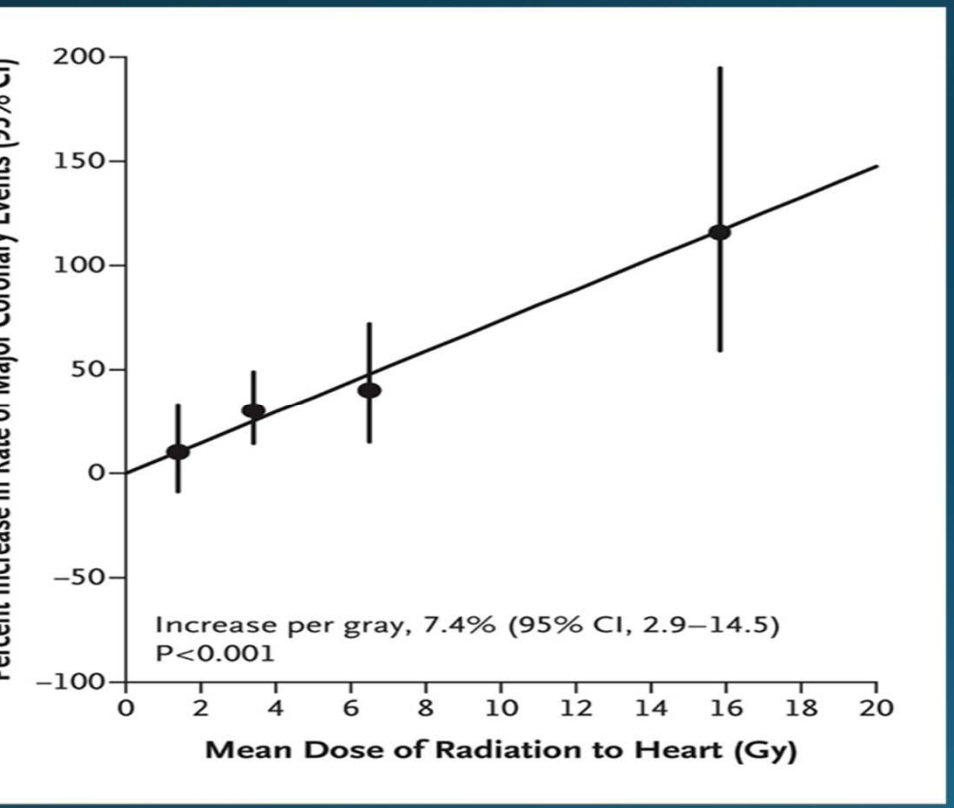
Factors	Appropriate	Cautionary	Unsuitable
Patient factors			
Age	≥ 50 yr < 50 yr with boost	< 50 yr (without boost)	
Pathologic factors			
T stage	T1–2	T3	T4
N stage	N0	N1	N2+
Margins	Negative		
Grade	1–2 3 (with boost)	3 (without boost)	
Receptor status	ER/PR-positive/negative	HER2-positive Triple-negative	HER2-positive (with concurrent trastuzumab)
Histology	Invasive carcinoma	DCIS	Inflammatory
Treatment factors			
Surgery	Breast-conserving	Mastectomy	Breast reconstruction
Chemotherapy	None	Neoadjuvant Adjuvant	Concurrent
Dose inhomogeneity	≤ ±7% MP	±7% MP to ± 10% 3D	Concurrent

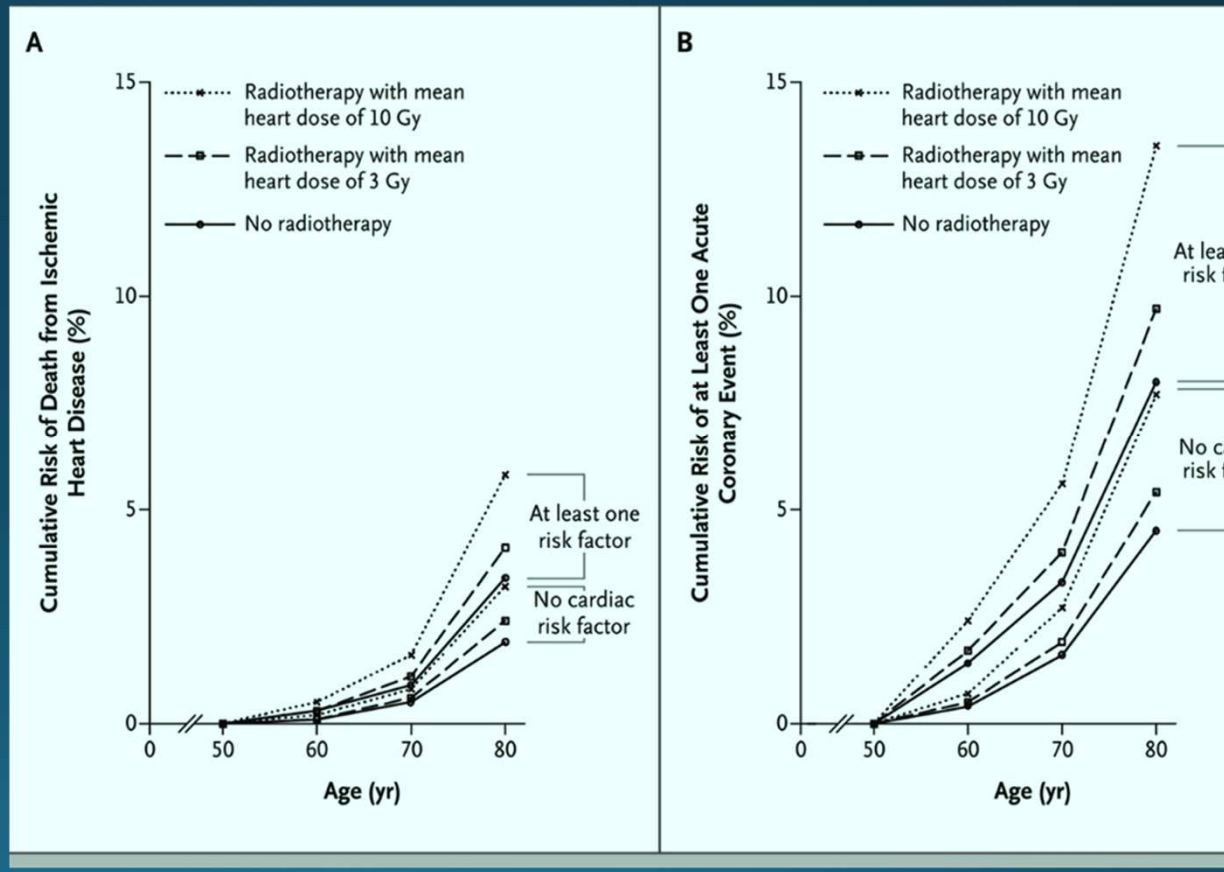
3D = three-dimensional conformal therapy; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor type 2; MP = at midplane; PR = progesterone receptor; START = Standardisation of Breast Radiotherapy trial.

Concerns with Hypofractionation

- Cardiac morbidity
- RNI and Brachial plexopathy
- Large breast
- High grade tumors
- DCIS
- Post mastectomy
- Systemic therapies

Cardiac toxicity





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International Journal of Radiation Oncology*Biology*Physics

Volume 88, Issue 4, 15 March 2014, Pages 786–792

Clinical Investigation

Adjuvant Hypofractionated Versus Conventional Whole Breast Radiation Therapy for Early-Stage Breast Cancer: Long-Term Hospital-Related Morbidity From Cardiac Causes

This work was presented at the 2013 San Antonio Breast Cancer Symposium, December 4-8, 2012; San Antonio, TX.

Elisa K. Chan, MD*, Ryan Woods, MSc†, Mary L. McBride, MSc†, Sean Virani, MD‡, Alan Nichol, MD§, Caroline Speers, BA‖, Elaine S. Wai, MD§, Scott Tyldesley, MD§,

- *Conclusion-*

  No difference in morbidity from cardiac causes among women with left sided early breast cancer treated with –WBI or CF WBI at 15 yrs f/u.

REGIONAL NODAL IRRADIATION

REGIMEN	EQUIVALENT TOTAL DOSE(Gy)in 2Gy /#		
	α/β=3Gy	α/β=2Gy	α/β=1.5Gy
40Gy/15F	45.5	46.7	47.6

Regional nodal irradiation

Aim –

To determine whether hypofractionated schemes increased the risk of damage to healthy tissues, particularly the brachial plexus.

13 studies

Conclusion when the dose below an EQD2 of 50, the risk of Brachial Plexopathy was < 1%

Ca1ecki J, et al Radiation-induced brachial plexopathy and hypofractionated regimens inAdjuvant irradiation of patients with breast cancer a review. Acta Oncol 2006;45(3):280e4

? ARM EDEMA

- Hypofractionated regimens without compensatory decrease in total dose may lead to increased rates of arm oedema.

❖ One retrospective comparison

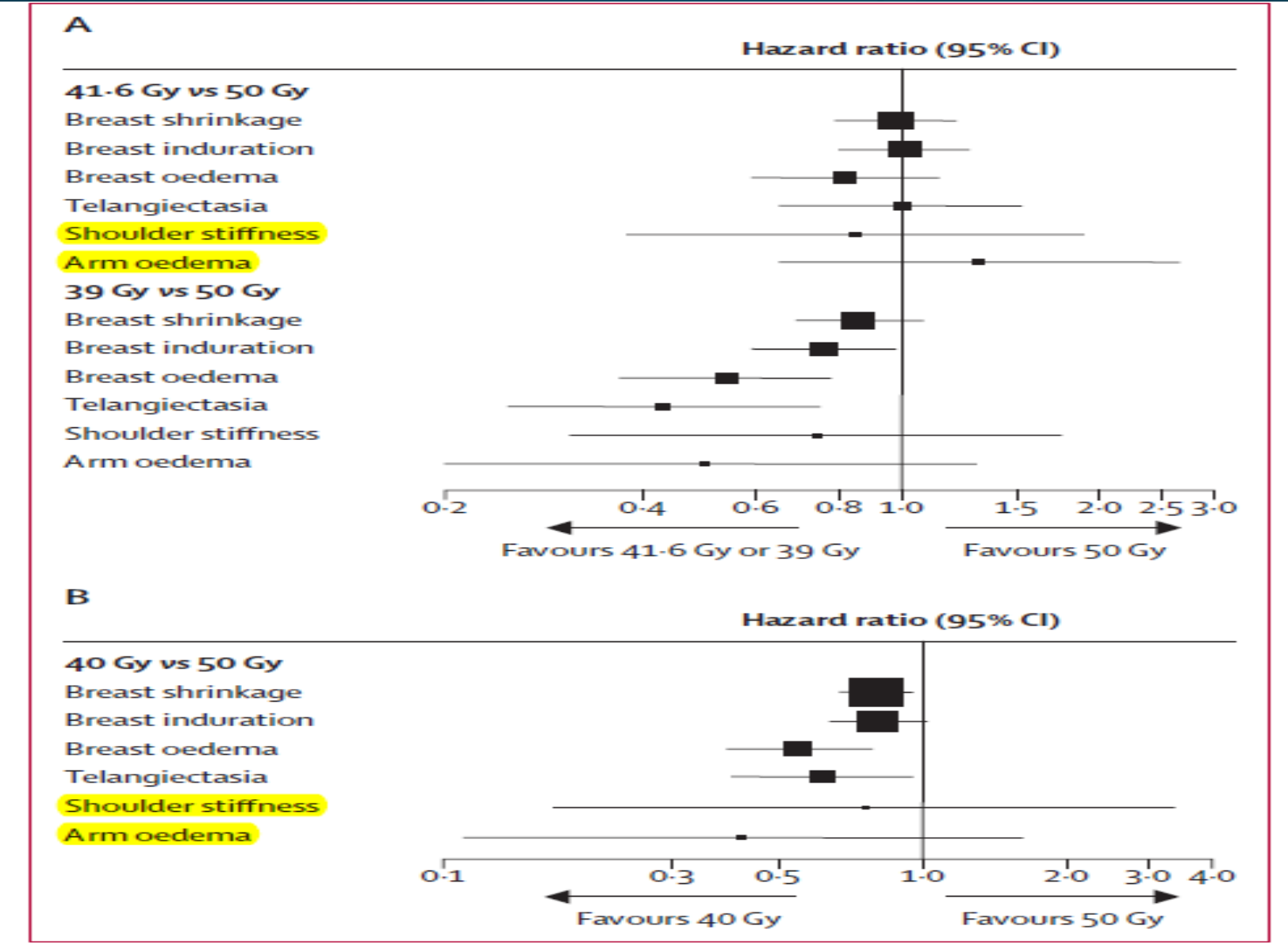
*55 to 60 Gy.

*15% Vs 6% to same total dose.

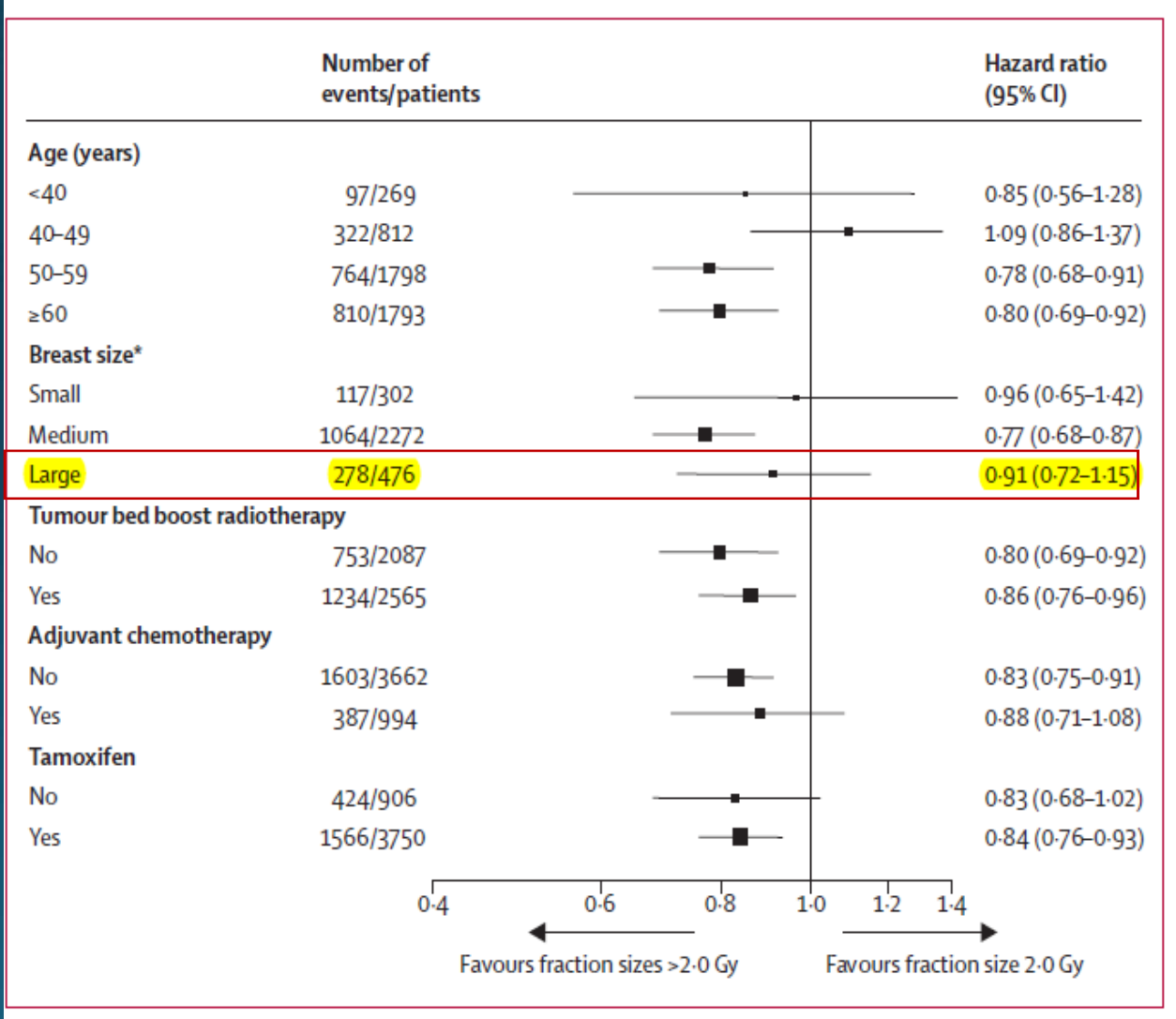
❖START trials – No significant increase in arm edema

- *Fehlauer et al Late effects and cosmetic results of conv vs hypo irradiation in BCT Strahlenther Onkol 2005;181(10):625e31*

START TRIALS

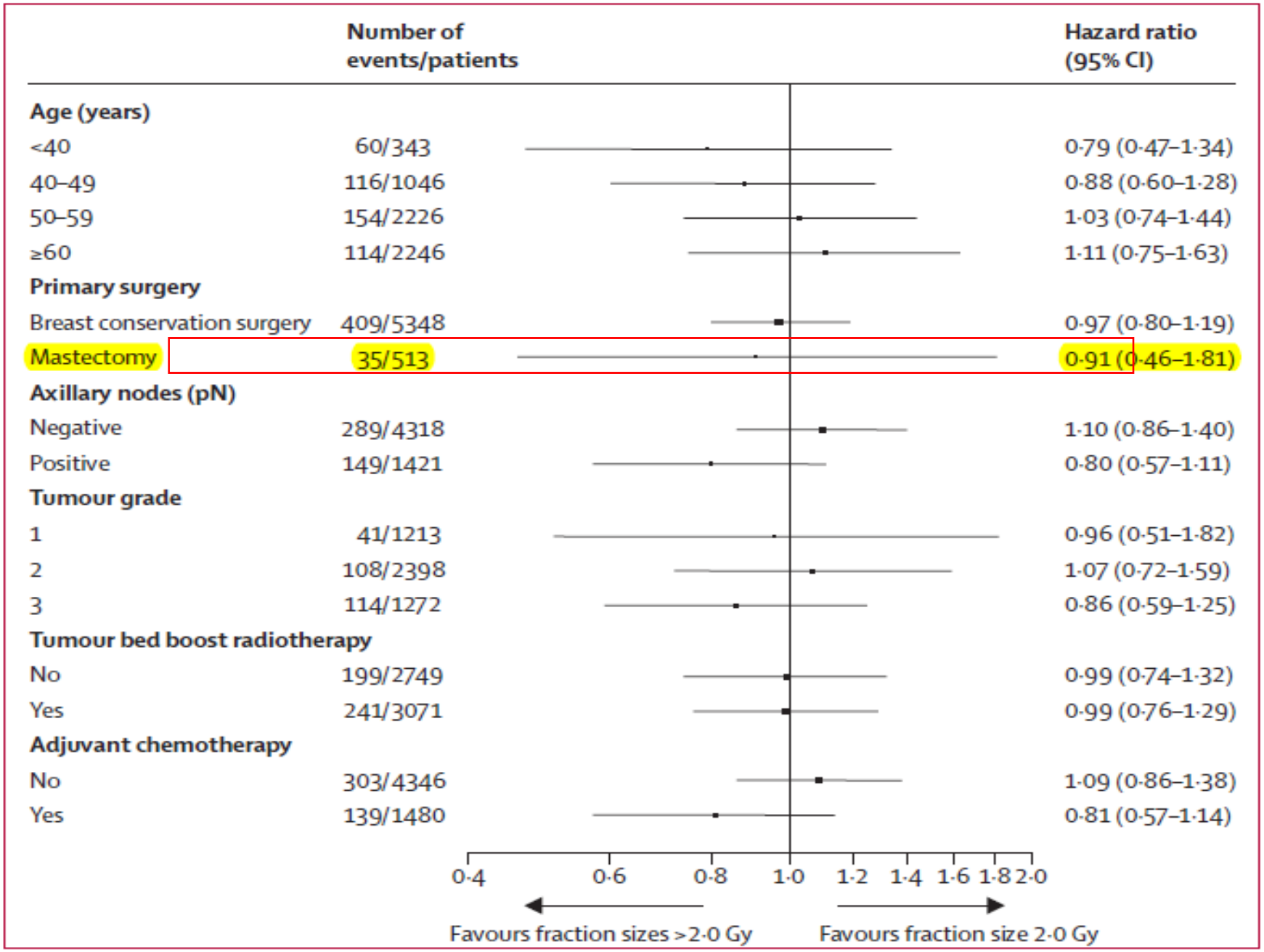


Large Breast: START TRIALS



Post Mastectomy RT

	Type of primary surgery	
	Breast-conserving surgery (n=848)	Mastectomy (n=232)
Change in skin appearance since radiotherapy		
50 Gy	1	1
41·6 Gy	0·92 (0·68–1·25)	0·53 (0·28–0·99)
39 Gy	0·63 (0·45–0·88)	0·64 (0·34–1·17)
Skin problems on or in area of affected breast†		
50 Gy	1	1
41·6 Gy	1·02 (0·70–1·50)	0·90 (0·39–2·10)
39 Gy	0·87 (0·58–1·30)	1·07 (0·48–2·38)
Pain in area of affected breast†		
50 Gy	1	1
41·6 Gy	1·29 (0·92–1·82)	0·82 (0·42–1·61)
39 Gy	1·01 (0·70–1·45)	0·87 (0·45–1·69)


Number of events/patients
Hazard ratio (95% CI)
Age (years)
<40 60/343 0·79 (0·47–1·34)
40–49 116/1046 0·88 (0·60–1·28)
50–59 154/2226 1·03 (0·74–1·44)
≥60 114/2246 1·11 (0·75–1·63)
Primary surgery
Breast conservation surgery 409/5348 0·97 (0·80–1·19)
Mastectomy 35/513 0·91 (0·46–1·81)
Axillary nodes (pN)
Negative 289/4318 1·10 (0·86–1·40)
Positive 149/1421 0·80 (0·57–1·11)
Tumour grade
1 41/1213 0·96 (0·51–1·82)
2 108/2398 1·07 (0·72–1·59)
3 114/1272 0·86 (0·59–1·25)
Tumour bed boost radiotherapy
No 199/2749 0·99 (0·74–1·32)
Yes 241/3071 0·99 (0·76–1·29)
Adjuvant chemotherapy
No 303/4346 1·09 (0·86–1·38)
Yes 139/1480 0·81 (0·57–1·14)
0·4 0·6 0·8 1·0 1·2 1·4 1·6 1·8 2·0
Favours fraction sizes >2·0 Gy
Favours fraction size 2·0 Gy

Age < 50 years

- < 50 yrs - LR Risk ⬆
- EBCTG – LR: 20-35% at 10 yrs

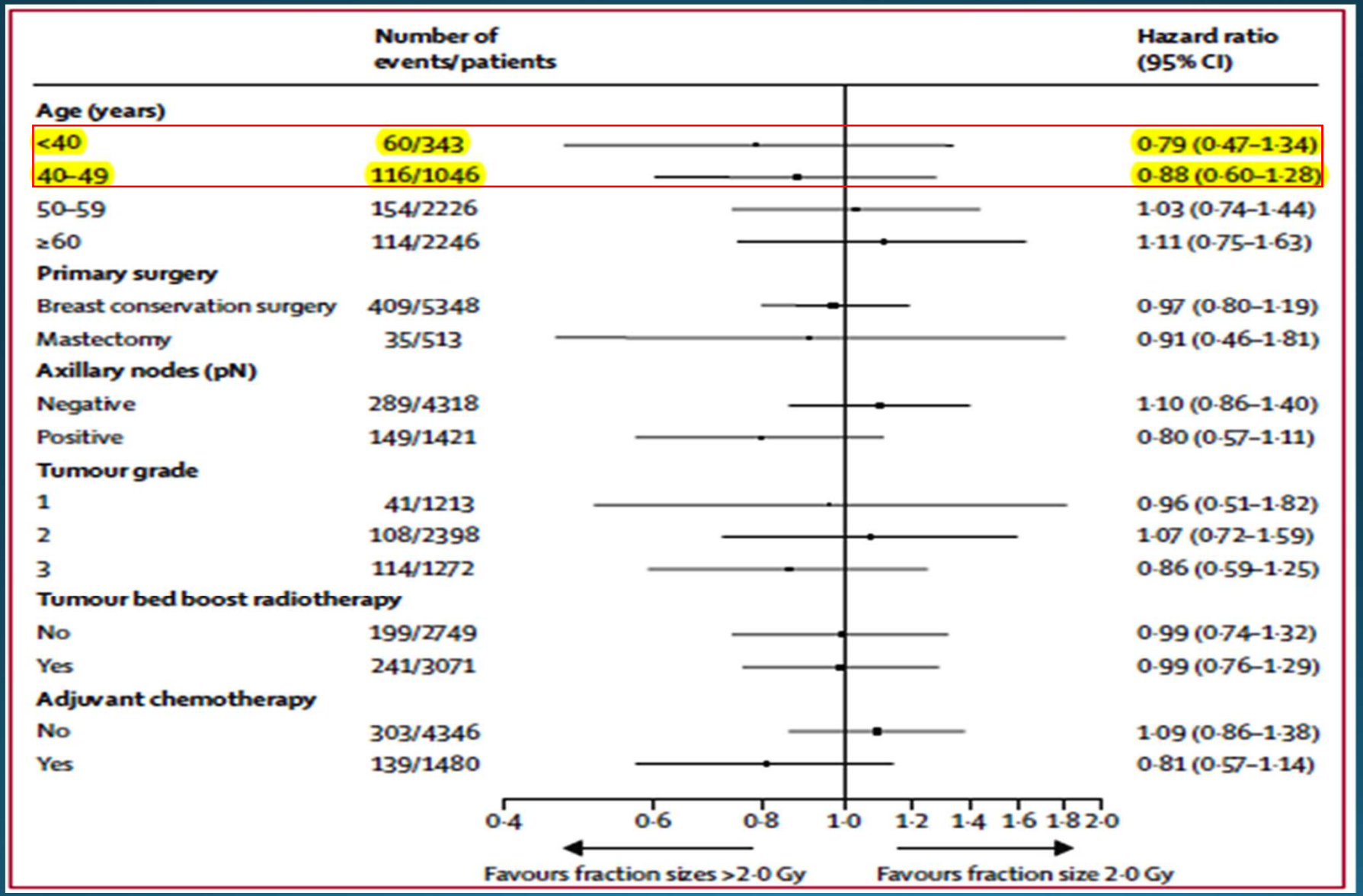
- ASTRO (2011) Guidelines –

  Hypo#: Not recommended for patients, < age 50years .

- Canadian study –

  stratified by age (RR - 4% and 7%) - without boost

START TRIALS



High-grade tumors

- High grade → high LR
- LR - 28.6% in the EBCTCG meta-analysis.
- Canadian study- 233 pts with grade 3 tumors, LF- 15.6% vs 4.7% ([HR] = 3.08; P = .01)
- No boost / CT

Canadian Trial

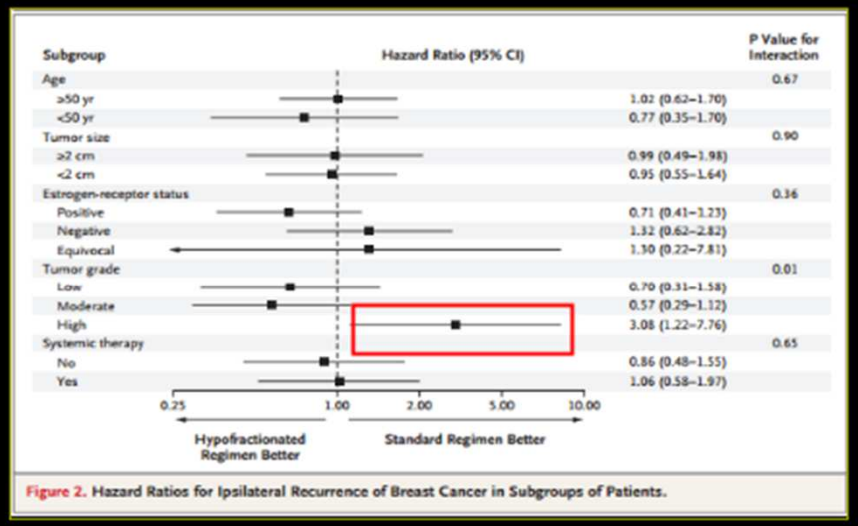


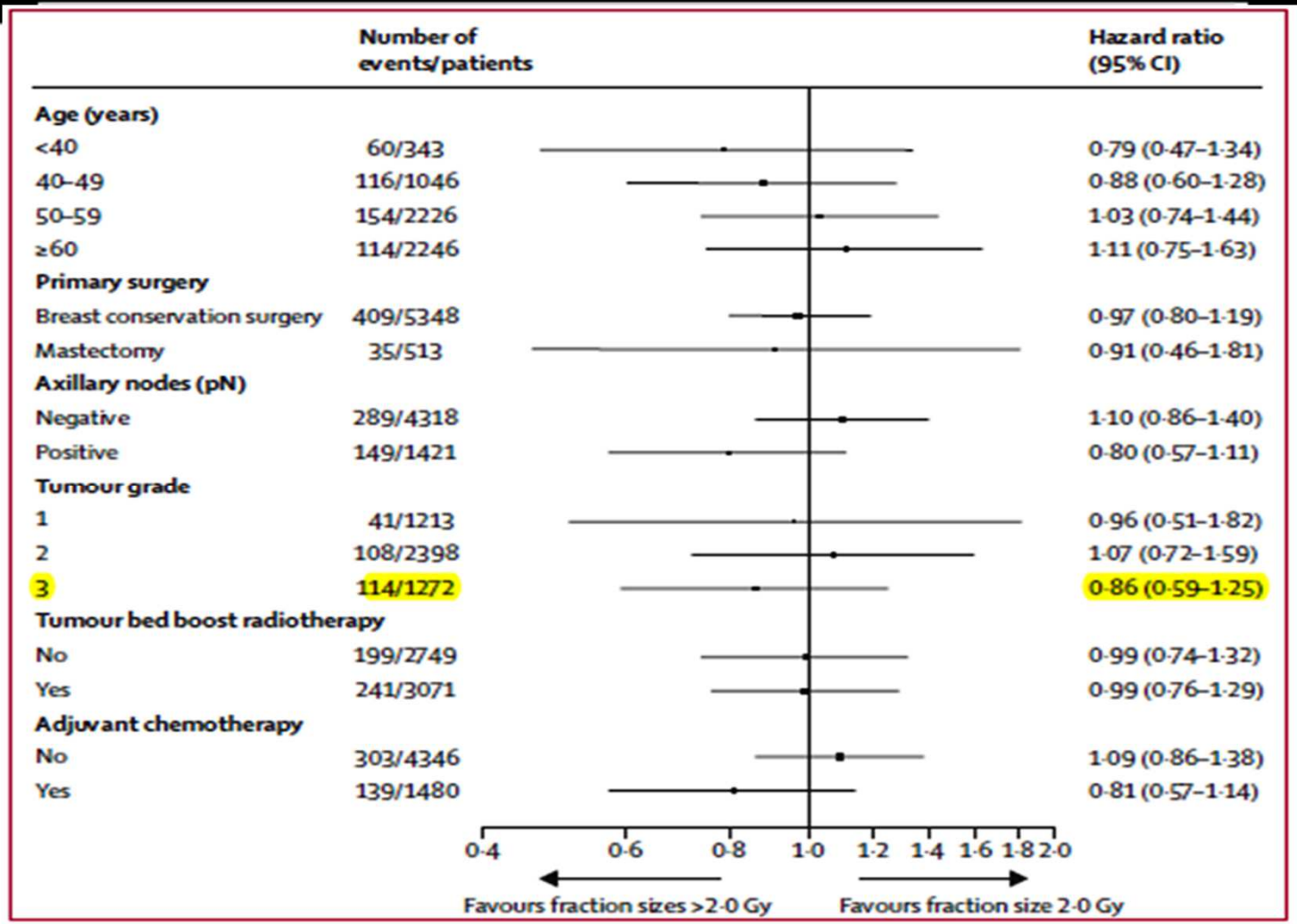
Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

Limitations:
-most women >50y,
- <T1,
-ER+ and Grade I-II
- all were pN0,
-few patients received chemotherapy (? May increase toxicity)

Unplanned sub-group analysis of high-grade tumors: 10-yr LR 4.7% (50Gy) 15.6% (42.5Gy);

START

Patients eligible for hypofractionation



Meta-analysis of all START trials did not show a higher rate of relapse with Grade 3 tumors (vs. Whelan trial)

HF and Chemotherapy

- > 1600 pts received systemic chemo in the randomized trials
- No increased toxicity
- Evidence lacking for safety of neo-adjuvant chemo and Hypofractionation
- No evidence in patients receiving Traztuzumab

Cancer

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Original Article

Longitudinal analysis of patient-reported outcomes and cosmesis in a randomized trial of conventionally fractionated versus hypofractionated whole-breast irradiation

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In this randomized trial, longitudinal outcomes did not appear to differ by treatment arm. Patient-reported functional and pain outcomes improved over time. These findings are relevant when counseling patients regarding decisions concerning radiotherapy. ***Cancer* 2016.** *© 2016 American Cancer Society.* ***Cancer 2016;122:2886–2894.*** *© 2016 American Cancer Society*

Table 5 Ongoing Randomized Trials Evaluating Treatment With Hypofractionated vs Conventional Whole Breast Irradiation

Trial (Target Accrual)	Control Treatment Scheme (Gy/fxs)	Test Treatment Scheme (Gy/fxs)	Patient Population	Primary Endpoint
TROG 07.01 [61] (1,600)	50/25 +/– boost (10/5)	42.5/16 +/– boost (10/4)	Surgery: BCS DCIS only	Local recurrence
RTOG 10-05 [62] (2,150)	50/25 or 42.7/16 sequential boost (12/6 or 14/7)	40/15 Concurrent boost (48/15)	Surgery: BCS p, yp stage I–II DCIS	IBTR
IMPORT HIGH [64] (840)	IMRT 40/15 + boost (16/8)	IMRT 36/15 concurrent boost (48/15 or 53/15)	Surgery: BCS T1–3, N0–1 At least 1 RF	Local control Induration
Chinese Academy of Medical Sciences [65] (1,072)	PMRT + SCLV 50/25 + boost (10/5)	PMRT + SCLV 43.5/15 + boost (8.7/3)	Surgery: TM + ALND cT3-4, cN2	Locoregional control
SHARE [66] (2,796)	50/25 + boost (16/8)	40/15 or 42.5/16 or APBI 40/10	Surgery: BCS pT1, N0	Local recurrence

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TARGETING CANCER CARE

Five Things Physicians and Patients Should Question

1

Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules.

- Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5–6 weeks, often followed by 1–2 weeks of boost therapy.
- Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (approximately 4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.

5

Don't routinely use intensity modulated radiotherapy (IMRT) to deliver whole breast radiotherapy as part of breast conservation therapy.

- Clinical trials have suggested lower rates of skin toxicity after using modern 3-D conformal techniques relative to older methods of 2-D planning.
- In these trials, the term "IMRT" has generally been applied to describe methods that are more accurately defined as field-in-field 3-D conformal radiotherapy.
- While IMRT may be of benefit in select cases where the anatomy is unusual, its routine use has not been demonstrated to provide significant clinical advantage.

Conclusions

- Hypofractionated RT with doses ranging from 2.6-3.2 Gy per fraction and total doses of 40-41.6 Gy appears to equal or better than conventional fractionation in terms of local control and toxicity
- HF is recommended for eligible patients of EBC (DCIS, T1-3, N0-1)
- Long term safety data for Regional Nodal Irradiation is awaited
- Cardiac shielding should be done in left sided cases
- Limited data in post mastectomy cases and younger pts
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