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Dose escalated simultaneous integrated boost radiotherapy for early breast cancer: 3-year adverse effects - IMPORT HIGH trial
(CRUK/06/003)

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On behalf of the IMPORT HIGH Trial Management Group

San Antonio Breast Cancer Symposium
Thursday 6th December, 2018

SAN ANTONIO BREAST CANCER SYMPOSIUM 2018 DECEMBER 4-8
HENRY B. GONZALEZ CONVENTION CENTER, SAN ANTONIO, TEXAS, USA

Dr. Coles has no relevant financial relationships with commercial interests to disclose.

BACKGROUND

- Women at high risk of breast cancer local relapse:
  - Whole breast RT + sequential tumour bed boost
  - Usually 2.0Gy/fraction
  - 4.5–6.5 weeks of RT
- Hypothesis: Increasing RT fraction *size* rather than fraction *number* is time-sparing, safe & effective way of delivering boost dose
- IMPORT HIGH: tests effects of simultaneous RT *escalation* to boost volume & *reducing* RT to low risk breast volumes & **RT completed in 3 weeks**

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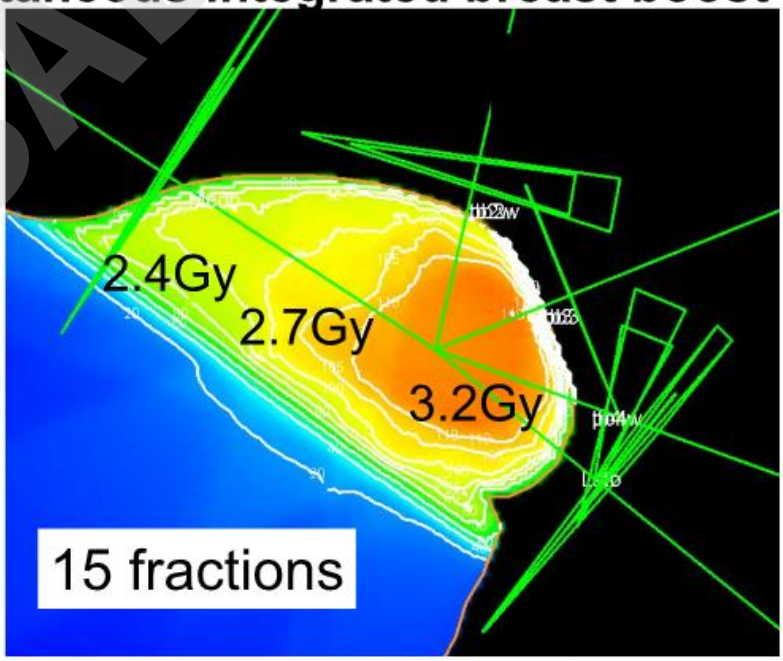
Risk adaptation of breast RT: high risk - simultaneous integrated breast boost (SIB)



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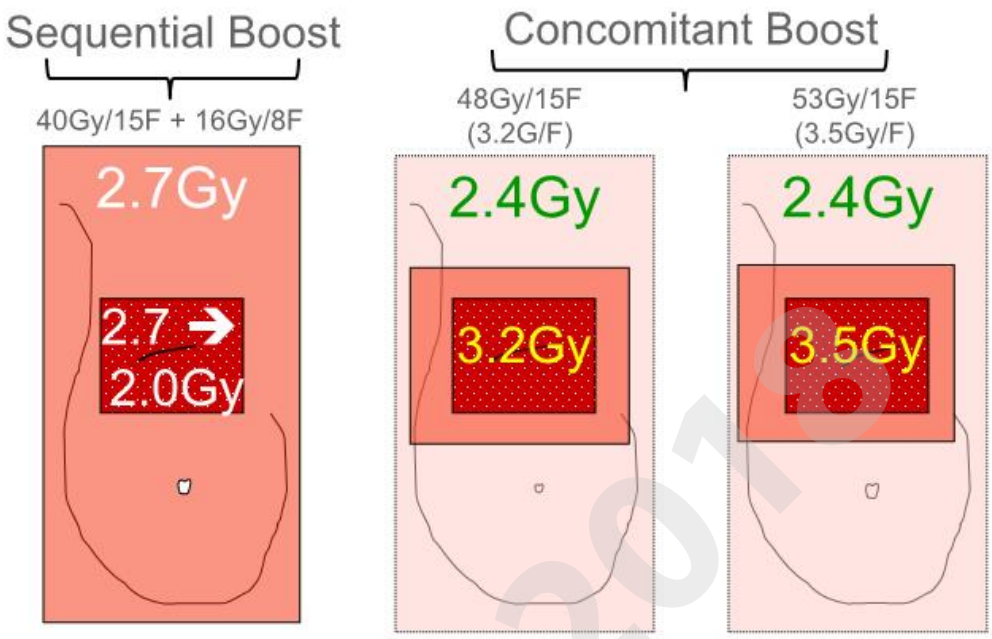
TRIAL DESIGN: Dose Escalated Intensity Modulated RT



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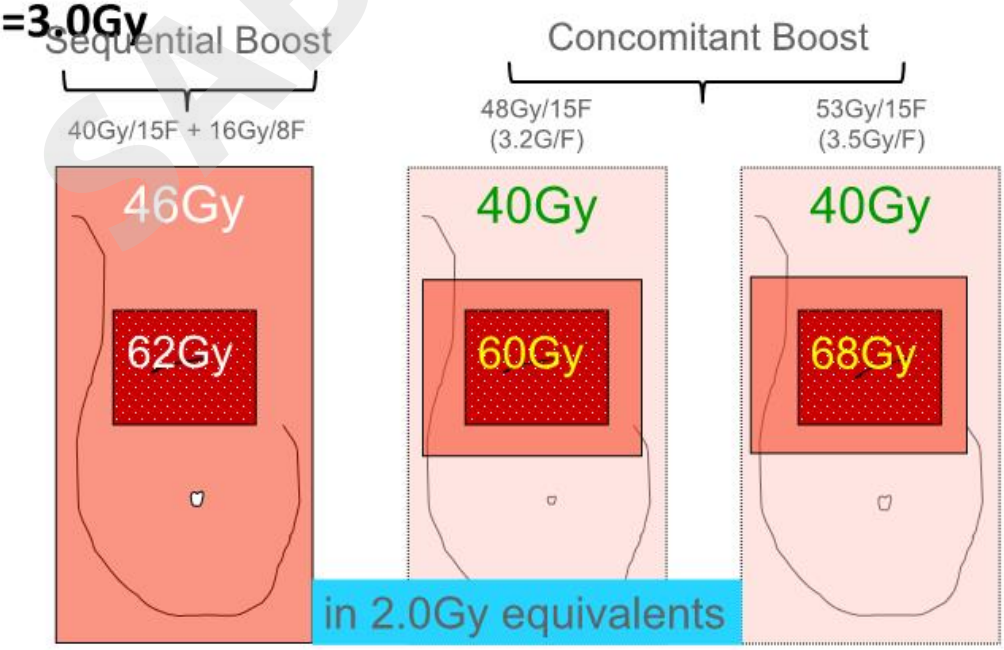
TRIAL DESIGN: Total Dose assuming α/β =3.0Gy



TRIAL DESIGN: Protocol adaptation

Eligibility criteria

- ***Patient requires tumour bed boost in addition to standard whole breast RT***
- Women age ≥18
- Breast conserving surgery
- pT1-3, pN0-pN3a, M0

Local relapse at 5 years

↓

Data expected 2020

Final protocol
N=2568
NORMAL TISSUE EFFECTS & TUMOUR RECURRENCE

- Local relapse (all patients)
- **PRO (n=840)**
- **Photographic assessment (n=840)**
- **CRO (all patients)**

Breast induration at 3 years

↓

Data mature and presented today

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TRIAL DESIGN: Sample size considerations

LOCAL RELAPSE: Non-inferiority of concomitant boost (both doses) vs sequential boost at 5 years (2568 patients; 856 per group)

NORMAL TISSUE EFFECTS: *Breast boost volume induration at 3 years* (840 patients; 280 per group)

- Principal comparison is between concomitant boost groups
  - 3.5Gy/F vs 3.2Gy/F boost dose
  - 80% power, 5% alpha (one-sided)
- ***Breast boost volume induration*** endpoint assumptions
  - 20% incidence in 53Gy/15F (3.5Gy/F) group
  - 7% *reduction* in 48Gy/15F (3.2Gy/F) group
- Comparisons with control group for interpolation as required

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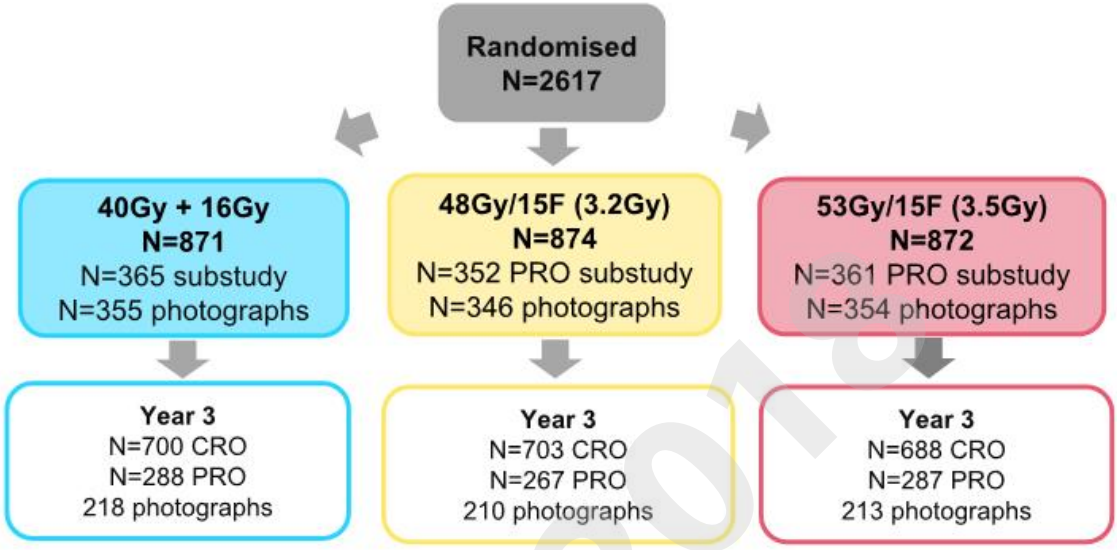
TRIAL DESIGN: Patient flow & endpoint data availability



- Median follow-up 58.9 (IQR 42.5-72.0) months

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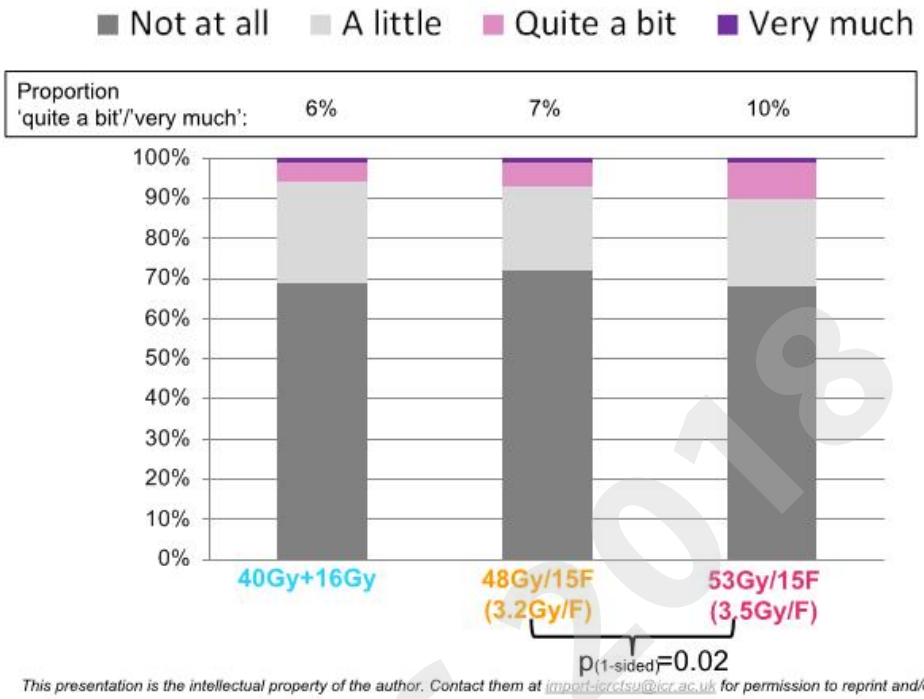
PATIENT CHARACTERISTICS: Baseline

		40Gy/15F + 16Gy/8F N=871	48Gy/15F (3.2Gy/F) N=874	53Gy/15F (3.5Gy/F) N=872
		n (%)	n (%)	n (%)
Age (years)	Median (IQR)	49 (45-56)	49 (45-55)	49 (44-57)
Tumour size (cm)	Median (IQR)	2.0 (1.5-2.8)	2.0 (1.5-2.7)	2.0 (1.5-2.7)
Grade	1	83 (10)	71 (8)	71 (8)
	2	340 (39)	310 (36)	329 (38)
	3	445 (51)	492 (56)	470 (54)
Pathological node status	Positive	260 (30)	268 (31)	251 (29)
	Negative	608 (70)	605 (69)	620 (71)
ER neg & HER2 neg		152 (18)	181 (21)	165 (19)
ER neg & HER2 pos		36 (4)	35 (4)	54 (6)
ER pos & HER2 neg		558 (64)	550 (63)	540 (62)
ER pos & HER2 pos		121 (14)	104 (12)	111 (13)

ENDPOINTS: CRO: *breast induration* at 3 years



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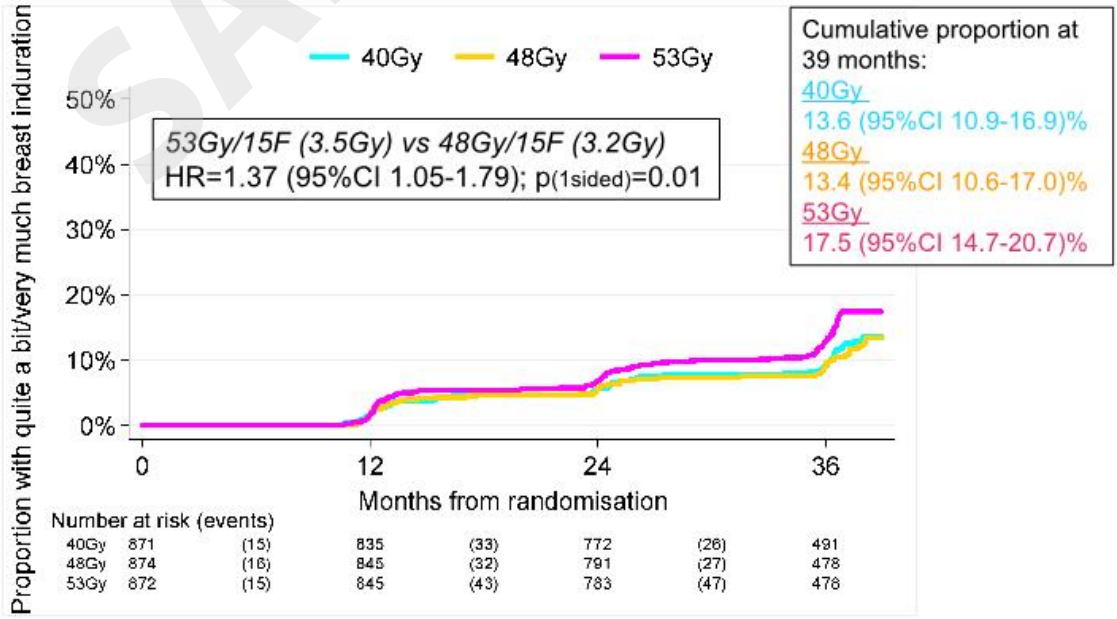
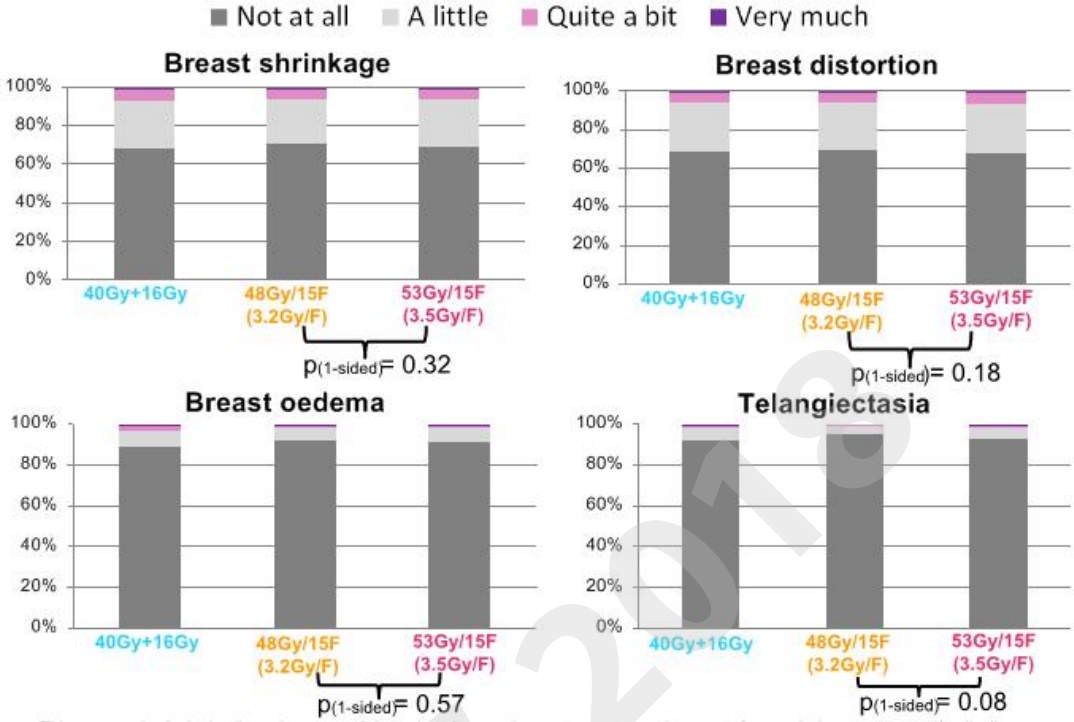
ENDPOINTS: CRO - Time to first *breast induration* event graded as 'quite a bit/very much'



ENDPOINTS: CRO - *Other* adverse effects at 3 years



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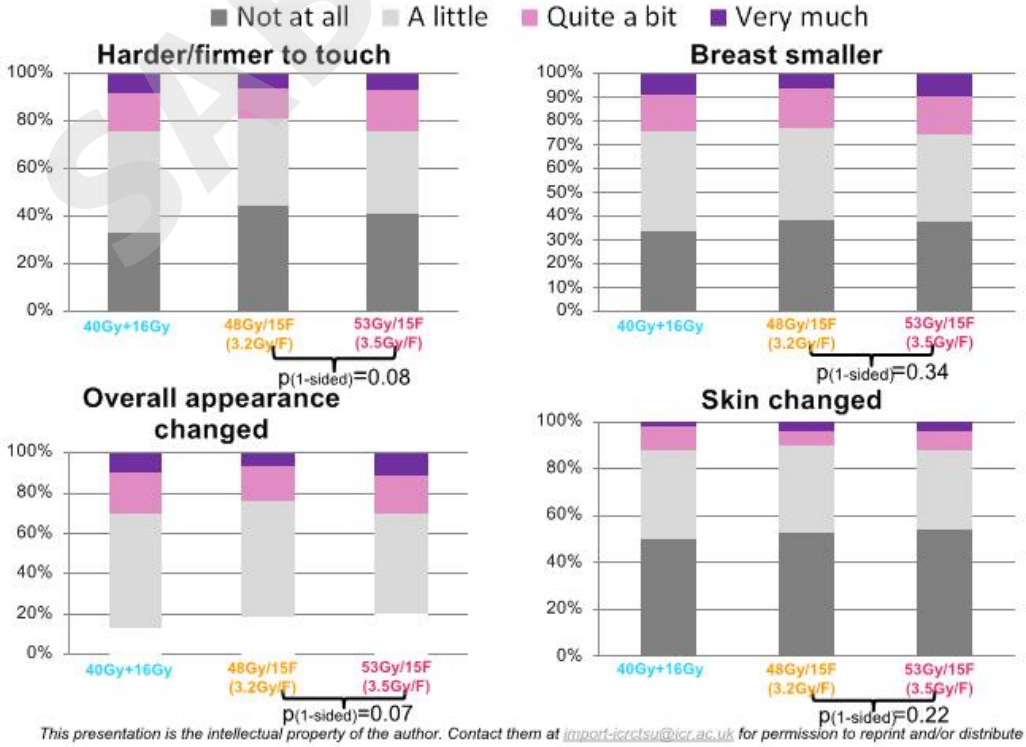
ENDPOINTS: PRO at 3 years



ENDPOINTS: Photographic outcomes at 3 years

Change in breast appearance	40Gy/15F + 16Gy/8F N=218	48Gy/15F (3.2Gy/F) N=210	53Gy/15F (3.5Gy/F) N=213
	n (%)	n (%)	n (%)
None	183 (84)	185 (88)	177 (83)
Mild	25 (11)	23 (11)	32 (15)
Marked	10 (5)	2 (1)	4 (2)

Fisher's Exact test none/mild vs marked:

- 53Gy vs 48Gy: $p_{(1\text{-sided})} = 0.35$

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CONCLUSIONS

- Largest & most mature reported adverse effects data of breast simultaneous boost within a clinical trial
- At 3 years, there is evidence of a dose response for adverse effects within the boost volume
- A SIB dose schedule is comparable to the control sequential boost schedule in terms of adverse effects
- Longer term follow-up & local relapse data needed before firm conclusions can be drawn regarding benefit or otherwise of dose-escalated IMRT SIB

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