"GBCC 2016"

Tumor Bed Boost Integration during Whole Breast Radiotherapy: A Review of the Current Evidence

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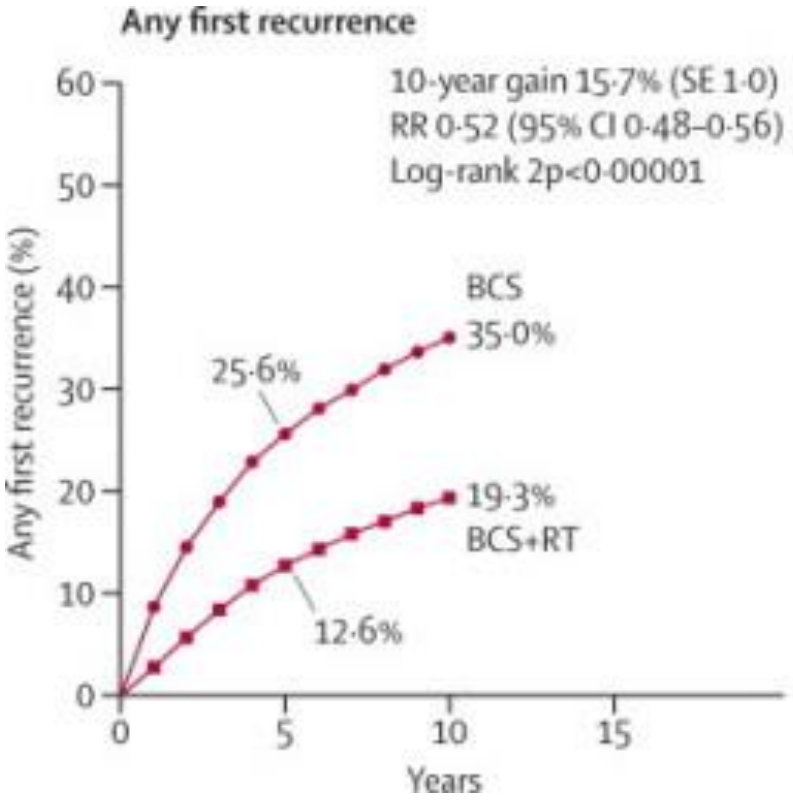
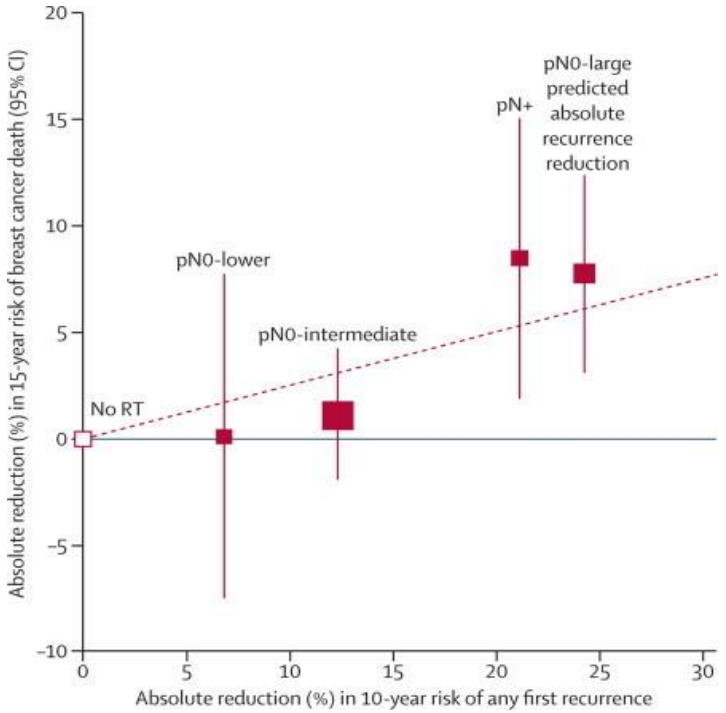
What I ‘m Talking About

- Review of Current Standard Whole Breast Radiotherapy & Tumor Bed Boost
- Introduction of SIB
- Scientific background of Simultaneous Integrated Boost (SIB)
- Current Status & Future Directions in SIB

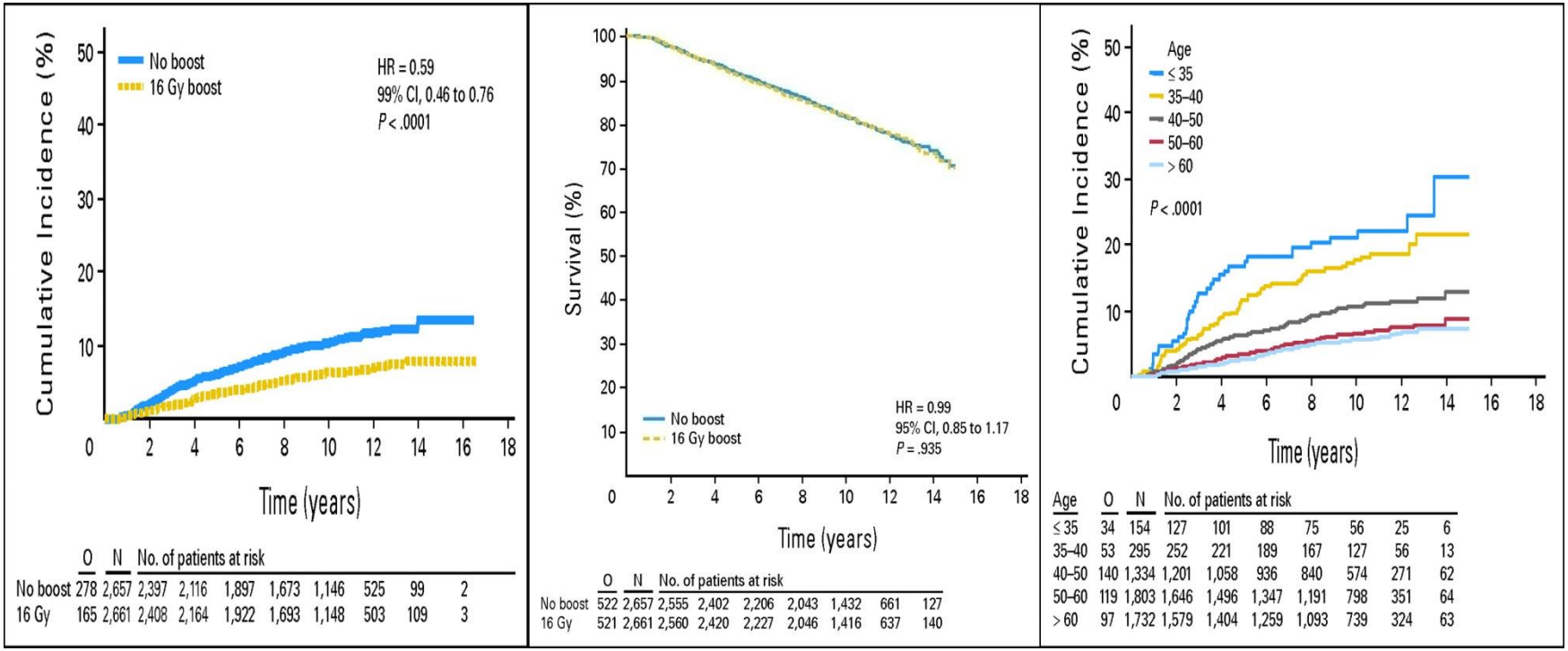
EBCTCG: Effect of RT after BCS 0n 10-yr recurrence and 15-yr breast cancer death





Lancet 2011;378:1707-16

Tumor boost: EORTC 22881-10882



- Bartelink, et al JCO 2007;25:3259-3265 -

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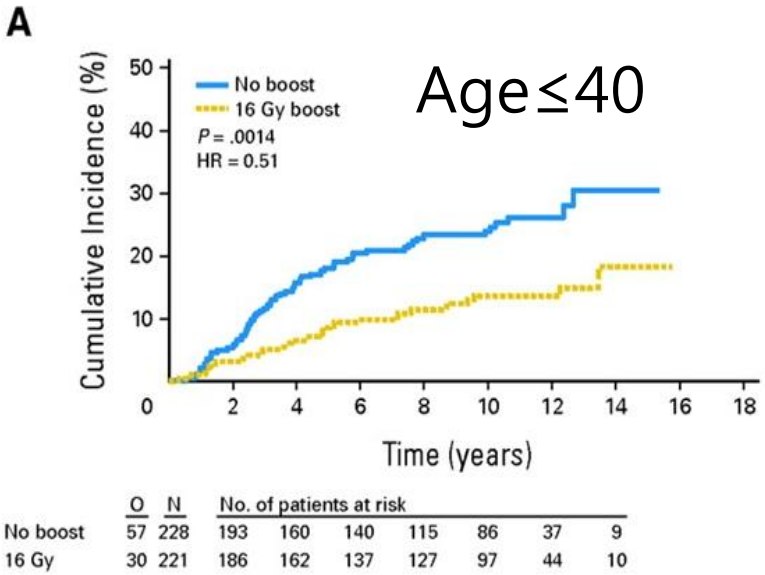
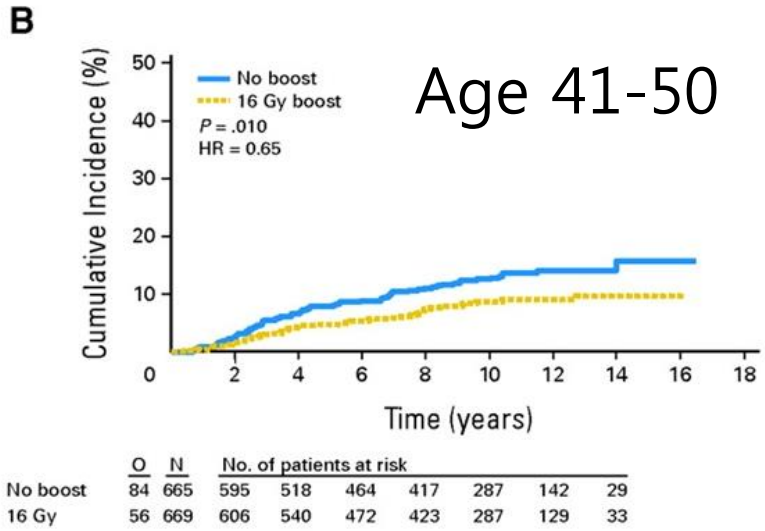
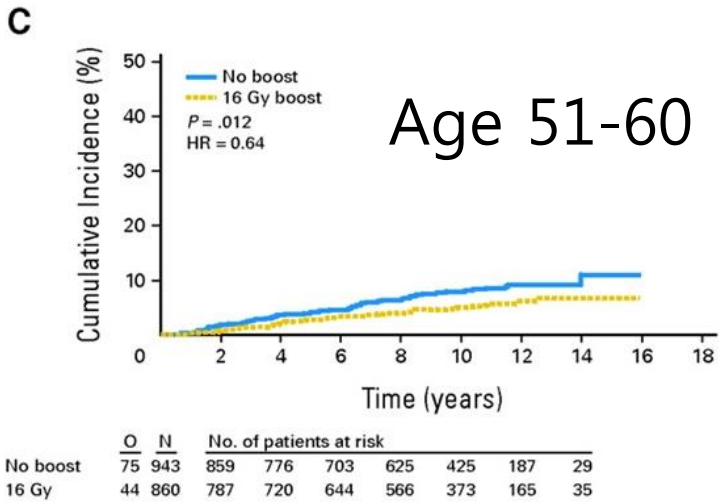
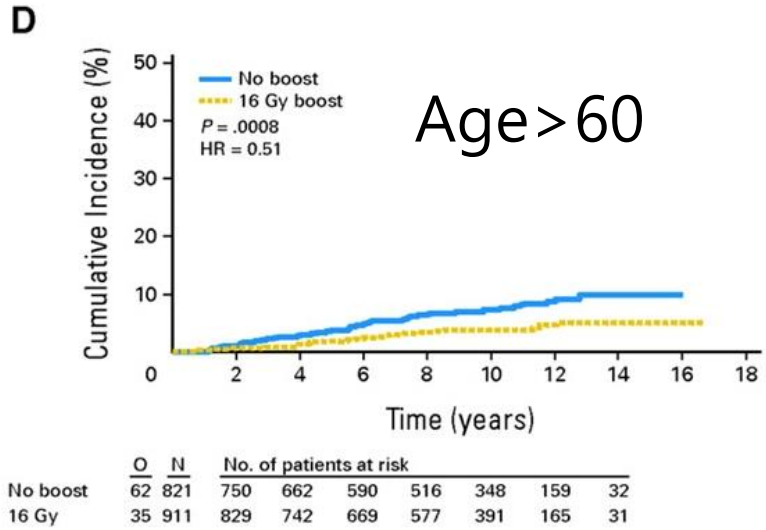








Postop. RT after BCS

- Whole breast Irradiation
- 50Gy/25fx
- +
- Tumor Boost
- 10-16Gy/5-8fx

Why was Hypofractionation introduced in Breast cancer?

- The aim of these studies was a more pragmatic one
- to decrease the number of visits to the RT department
- to shorten overall treatment time,
- thereby making adjuvant RT more convenient for patients.

Trials of Hypofactionation

	RMH/GOC	START A	START B	Canadian
site	UK	UK 2236	UK 2215	Canada 1234
Yrs accrual	1986 -98	1998-2002	1999-2001	1993-96
Standard arm	50Gy/25F	50Gy/25F	50Gy/25F	50Gy/25F
Exp. Arm	42.9Gy/13F/ 5w 39Gy/13F/ 5w	41.6Gy/13F/ 5w 39Gy/13F/ 5w	40Gy/15F /3w	42.5Gy/16F /3.2w

Trials of Hypofactionation

trials	patients	Local Recurrence(%)	Adverse Cosmesis(%)	
OCOG 2010	1234 , BCS pT1-2, pN0	6.7 6.2	29 30	Whelan et al, NEJM 2010 352:513-20
START A 2013	2236, BCS pT1-3, pN0-1	6.7 5.6 8.1	42 42 31	Haviland et al Lancet Oncol,2013 14:1086-94
START B 2013	2215, BCS pT1-3,pN0-1	5.2 3.8	40 33	Haviland et al Lancet Oncol,2013

Local Recurrence in BCT

Trial	yrs	subgroup	5Y IBTR		
			2Gy	Hypofraction	
OCOG	1993-1996	All WBI Age<50 T2	3.2 7.2 5.4	2.8 3.6 6.4	
START A	1998-2002	All WBI +60%boost Age<50 G3 N(+) Age<50 or G3 or N(+)	3.6 7.4 7.3 6.6 5.5	3.5 2.9 4.6 6.7 4.4	5.2 7.1 6.9 4 6.1
START B	1999-2001	All WBI +60%boost Age<50 G3 N(+) Age<50 or G3 or N(+)	3.3 4.8 7.6 7.7 5.6	2.2 4.1 3.9 4.4 3	
EORTC	1989-1996	Age≤ 40 Age 41-50 G3	10 6 7		

UK NICE Guideline 2009

- recommendation
- Use external beam radiotherapy giving **40Gy in 15 fractions** as standard practice for patients with early invasive breast cancer after BCS or mastectomy

NCCN 2016: Breast Radiation

- 45-50Gy in 23-25 fx. or 40-42.5Gy in 15-16 fx. for whole breast radiation
- Based on Convenience and the data from the START trials,
- **Short course of radiation therapy is the NCCN-preferred options.**

Scientific Rationale for Changing Fractionation Regimens

- α/β value of normal tissues for late reactions in 2 - 3Gy
- α/β value of Tumors and early reacting tissues in the range of ≥10Gy
- In order to protect the healthy tissue from late radiation effects, irradiation should be administered at low fraction size of < 2Gy
- Dogma that all tumors have high α/β value has been challenged over the past years
- If the α/β of the tumor is low, hypofractionated RT is advantageous

START-pilot & START A Trials

- Adverse effects (815 events/ 2263 pts)
  : α/β = **3.1**Gy (95% CI 2.0 – 4.2)

- Tumor Relapse (349 events/ 3646 pts)
  : α/β = **3.5**Gy (95% CI 1.2 – 5.7)

- Consistent with hypothesis that **2Gy fractions are as gentle on breast cancer** as on healthy tissues

Concerns in Tumor Boost

- HF-WBI alone is not appropriate in some patients who benefit from tumor boost

- What is the optimal method to deliver the boost to the tumor bed with hypofractionation, for those higher risk breast cancer cases requiring boost?

Boost in Randomized Trials of Hypo-WBI

study	Fractionation Schedule	%Boost	LR (%)	Cosmetic %G/Excel	Time points
Canadian		0 0	6.7 6.2	71.3 69.8	10years
START A	2Gy 10Gy/5fx	60.4 61 60.5	6.7 5.6 8.1	60 58 66	5 years
START B	2Gy 10Gy/5fx	41.4 43.8	5.2 3.8	61 66	5years

NCCN 2016: Boost Radiation

- A boost to the tumor bed is recommended in patients at higher risk for recurrence
- Age <50, high grade disease, or focally positive disease
- Typical boost doses are **10-16Gy in 2Gy per fractions.**

Introduction of SIB

- One of the next logical steps in shortening radiotherapy treatment courses for early-stage breast cancer is to use the advantage of standard yet sophisticated planning and treatment systems to integrate additional doses into the lumpectomy bed during the delivery of WBI (integrated boost).

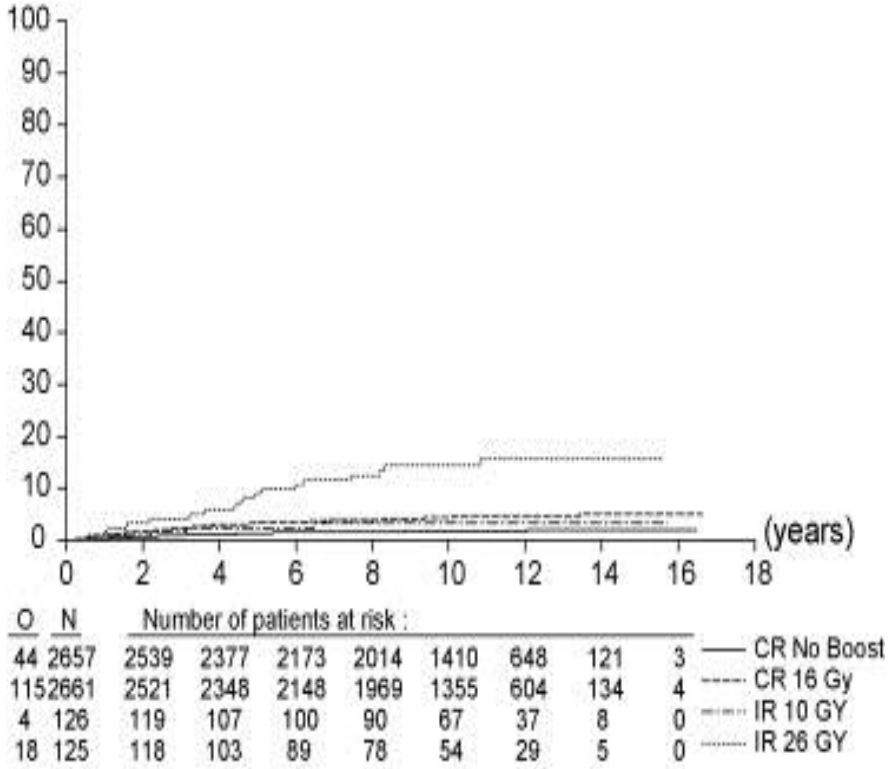
Technical Innovation

- Currently, IMRT is in widespread use by many centers worldwide.
- IMRT has been shown to reduce rates of acute radiation dermatitis during WBI.
- All the above mentioned studies were conducted prior to adoption of IMRT for treatment of breast cancer.
- IMRT might further decrease the risk of side-effects, consequently favoring the use of hypofractionated regimens.

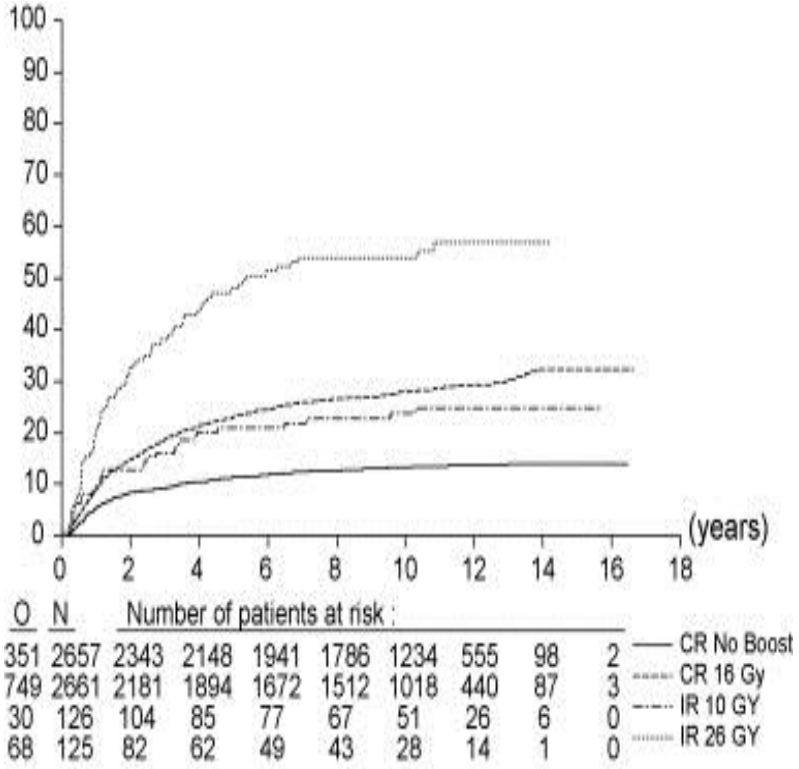
NCCN 2016: Breast Radiation

- The panel recommends whole breast irradiation be performed following CT-based treatment planning to limit irradiation exposure of the heart and lung, and to assure adequate coverage of the primary tumor and surgical site. Tissue wedging, forward planning with segments(step and shots), IMRT, respiratory gating, or prone positioning is recommended.

Tumor Bed Boost: EORTC 22881 Trial



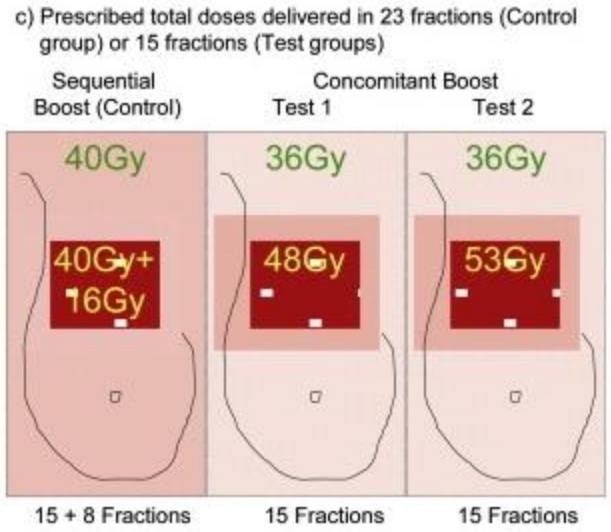
Severe fibrosis

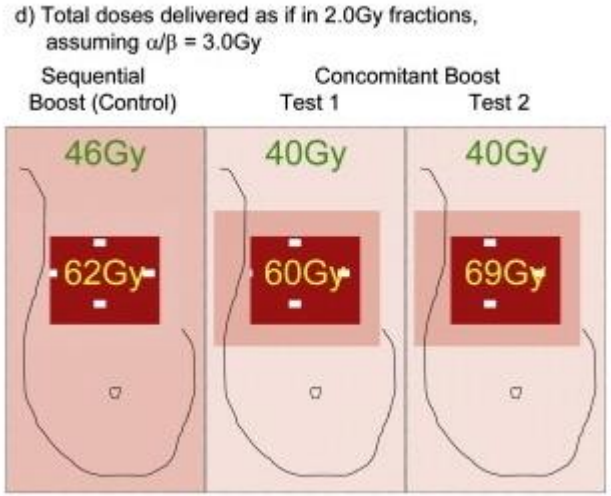


Moderate to Severe fibrosis

Decision on Dose Fractionation

- UK IMPORT High Trial (n=2568)





Control Test 1 Test 2 Control Test 1 Test 2

Radiobiologic Rationale

schedule	WB fractionation	Boost Fractionation	Total no. fractions	Nominal total dose	BED tumor control (α/β 4Gy)	BED acute effects (α/β 10Gy)	BED Late effects (α/β 3.4Gy)
CBRT	2.7	3.3	15	49.5	90.3	65.8	**97.5**
CBRT	2.7	3.2	15	48	86.4	63.4	**93.2**
H-SBT	2.7	2Gy * 8fx	23	56.1	90.8	69.9	**90.7**
H-SBT	2.7	2Gy * 5fx	20	50.1	81.5	62.8	**87.4**
C-SBT	2Gy	2Gy * 8fx	33	66	99	79.2	**105**
C-SBT	2Gy	2Gy * 5fx	30	60	90	72	**95.3**

Implementation of SIB in Hypofractionated Radiotherapy of Breast Cancer

	Scorsetti et al	Chada et al	Parijs et al	German multicenter trial
Phase/pts	I-II/50	I-II/160	I-II	II/141
RT tech	V-MAT	Linac	Tomo	Linac
F-U(median)	6m	3.5 Y		2Y
fractionation	15	15	15	16
Whole breast	40.5(2.7)	40.5(2.7)	42(2.8)	40(2.5)
SIB	48(3.2)	45(3.0)	51(3.4)	48(3.0)
Acute Skin Toxicity	G1(32pts) G3(1pt)	NS	No severe toxicity	No G3-4
Cosmetic Outcomes	feasible	No adverse effect	feasible	feasible
5-YDFS	-	97%		

RTOG 1005: a phase III trial of Accelerated Breast Irradiation with Hypofractionation plus Concurrent Boost vs Standard WBI plus Sequential Boost for Early-Stage Breast Cancer

STRATIFY

Age
<50 vs. ≥50

Chemothe.
Yes vs. No

ER Status
+ vs. –

Histologic Grade
1,2 vs. 3

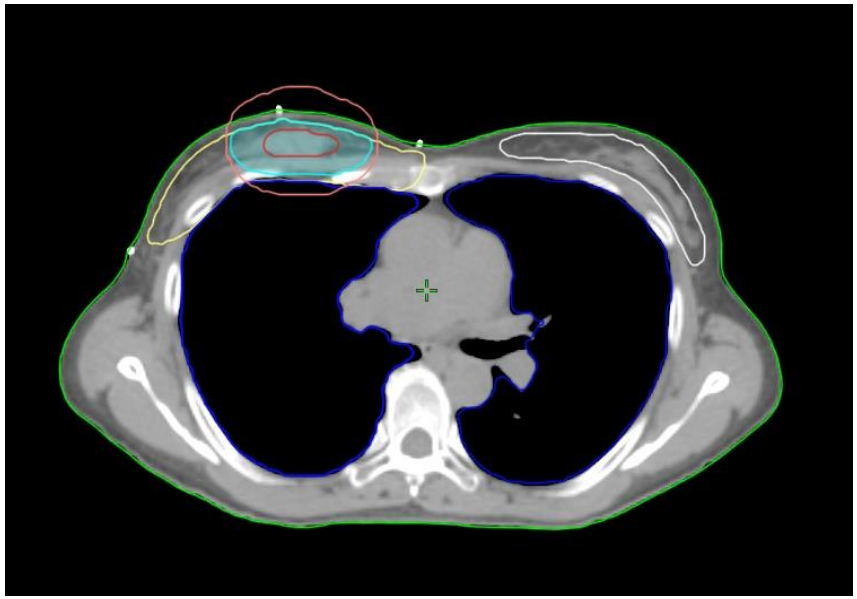
RANDOMIZE

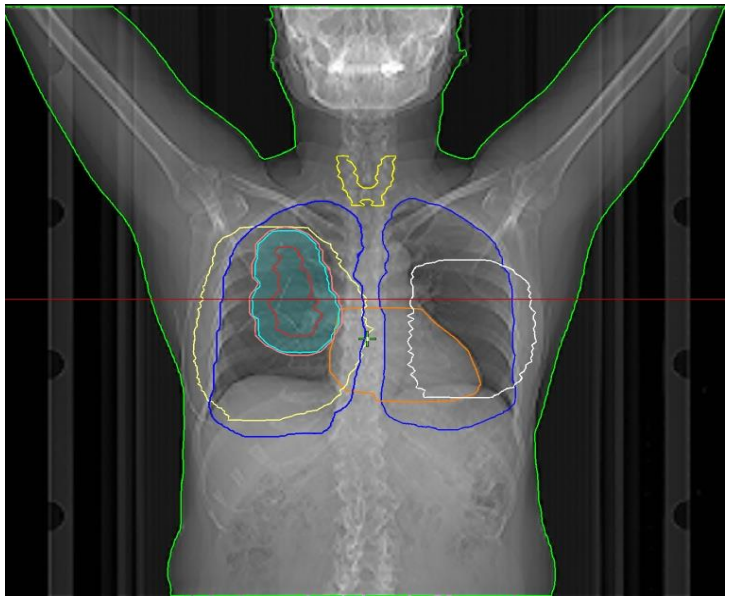
ARM 1: Standard fractionation
Whole Breast 50.0Gy/25 fractions/2.0Gy daily
Optional fractionation of 42.7Gy in 16 fractions permissible
Sequential Boost 12Gy/6/2.0Gy daily or 14.0Gy/7fx/2.0Gy daily

ARM 2: Hypofractionation (15fractions total)
Whole breast 40Gy/15 fx/2.67Gy daily
Concurrent Boost 48.0Gy/3.2Gy daily

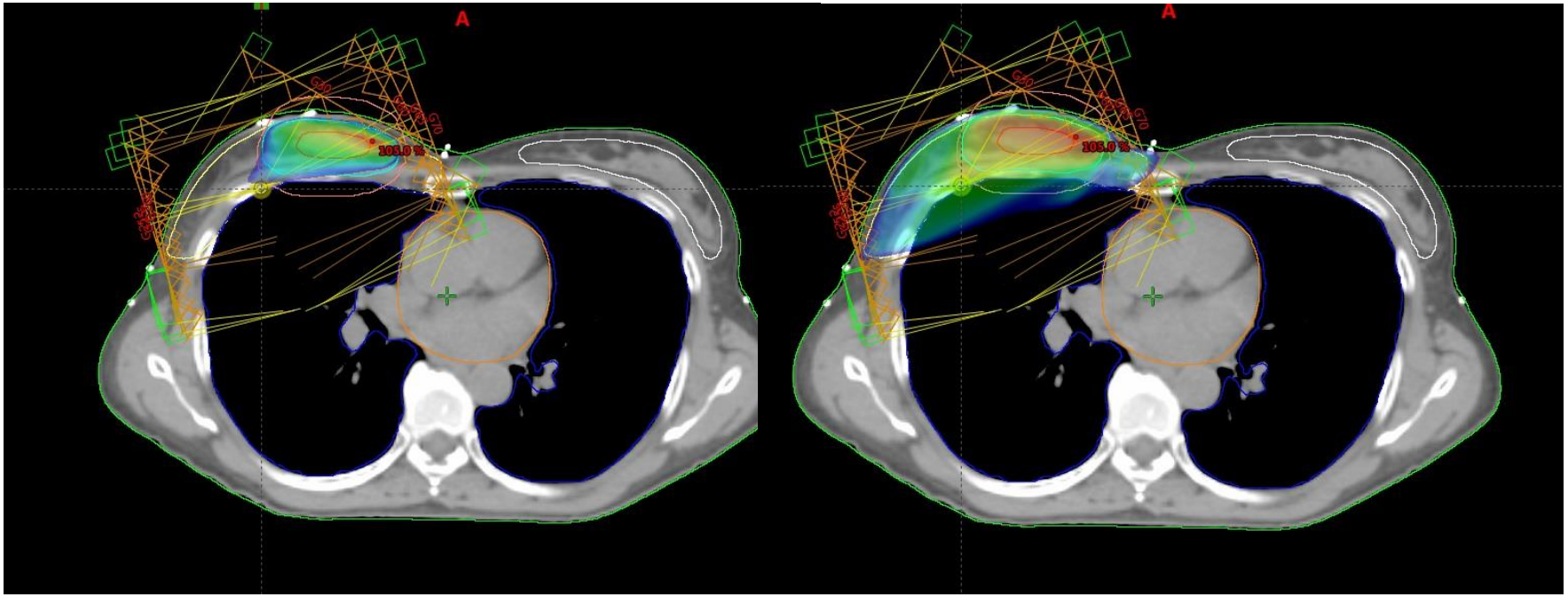
Definition of Target Volume & OAR

- RTOG 1005
- Lumpectomy Volume





Treatment Planning - SIB



1. PTV = 3.2Gy * 15fx. = 48Gy
2. CTV = 2.67Gy * 15fx. = 40Gy
3. Ipsilat. Lung, V16<15%
4. Heart, V16<5%, LT-side, RT
5. Contra breast, Dmax< 2.4Gy

1. PTV = 3.4Gy * 15fx. = 51Gy
2. CTV = 2.8Gy * 15fx. =42Gy
3. Ipsilateral Lung, V17<7%
4. Heart, V5<10%
5. Contralat. Breast, V10<5%

FAST Forward Trial: WB or CW(n=4000)

Trial group	Fx. size	TD	Fractions	Time (wk)
control	2.67	40	15	3
Test 1	5.4	27	5	1
Test 2	5.2	26	5	1
Iso-effective with control assuming α/β = 3Gy				

Paradigm Shift

- WBRT
- Boost

- Hypo-fx
- SIB

Equal Tumor control & cosmesis

Conclusions

- Breast cancer is as sensitive to fraction size as the dose-limiting normal tissues
- There is now a clear radiobiologic basis for the use of moderate hypofractionation, 15-16fx.
- Hypofractionated RT for breast cancer is becoming increasingly important.
- Delivery of a tumor bed boost in the form of SIB seems to be safe, feasible, and effective without compromising established excellent overall results.
- RTOG 1005 & The new HYPOSIB trial will clarify the question of SIB application using hypofractionation.