Reduced duration for Breast Cancer Radiotherapy

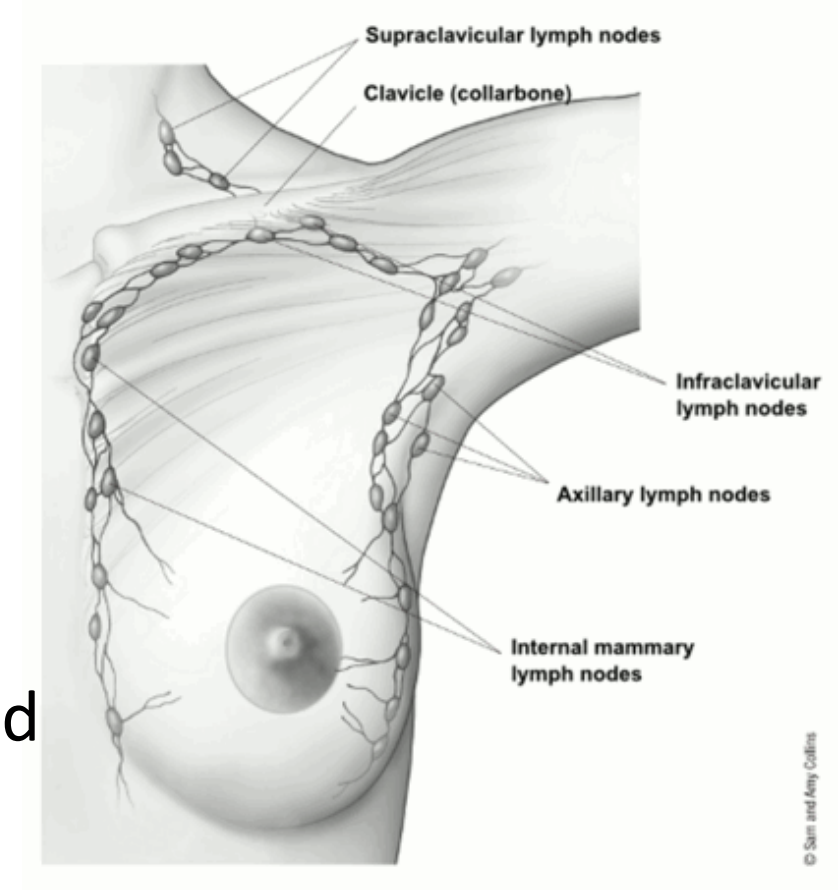
Poompis Pattaranutaporn, MD.

Breast Cancer

Role of Radiation

- After Mastectomy
  - T3 or T4
  - N+ >3 (N2)
- After Breast Conservative Surgery

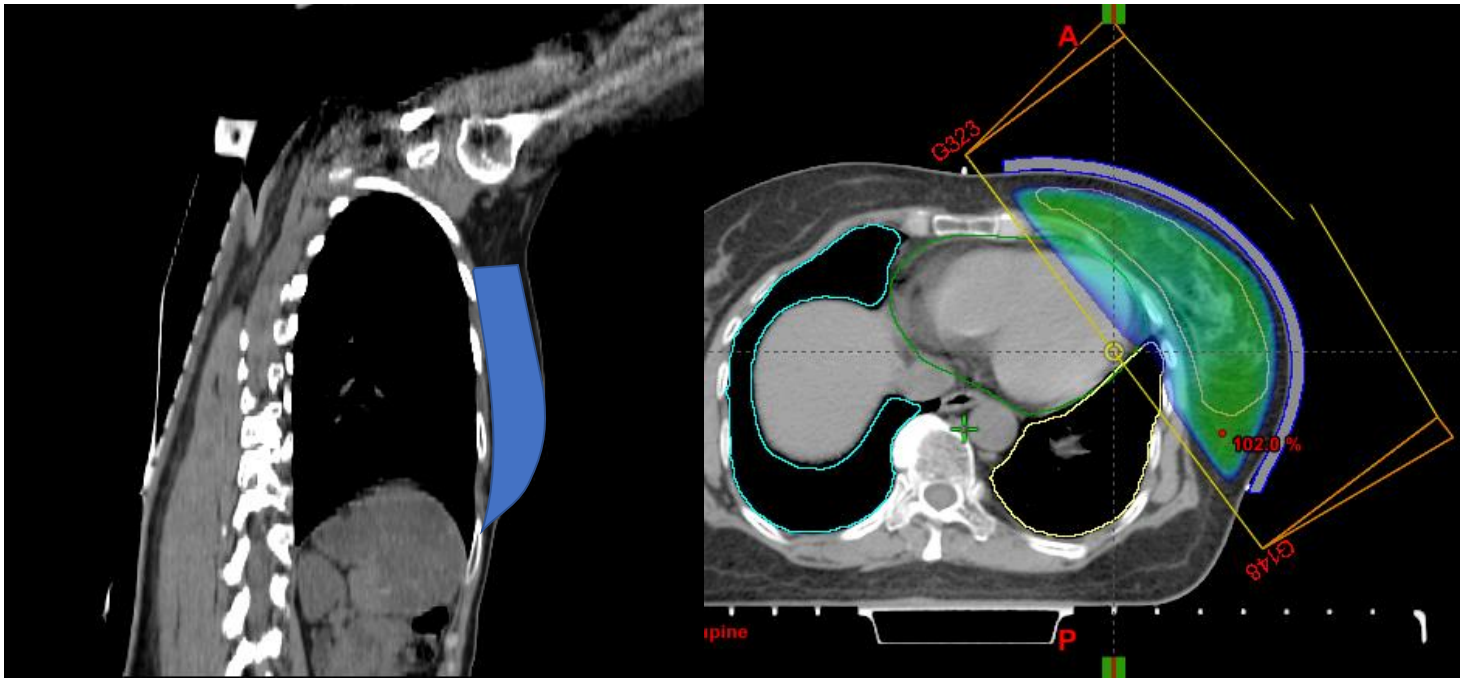
Radiation would eradicate the microscopic diseases and prevent local recurrence



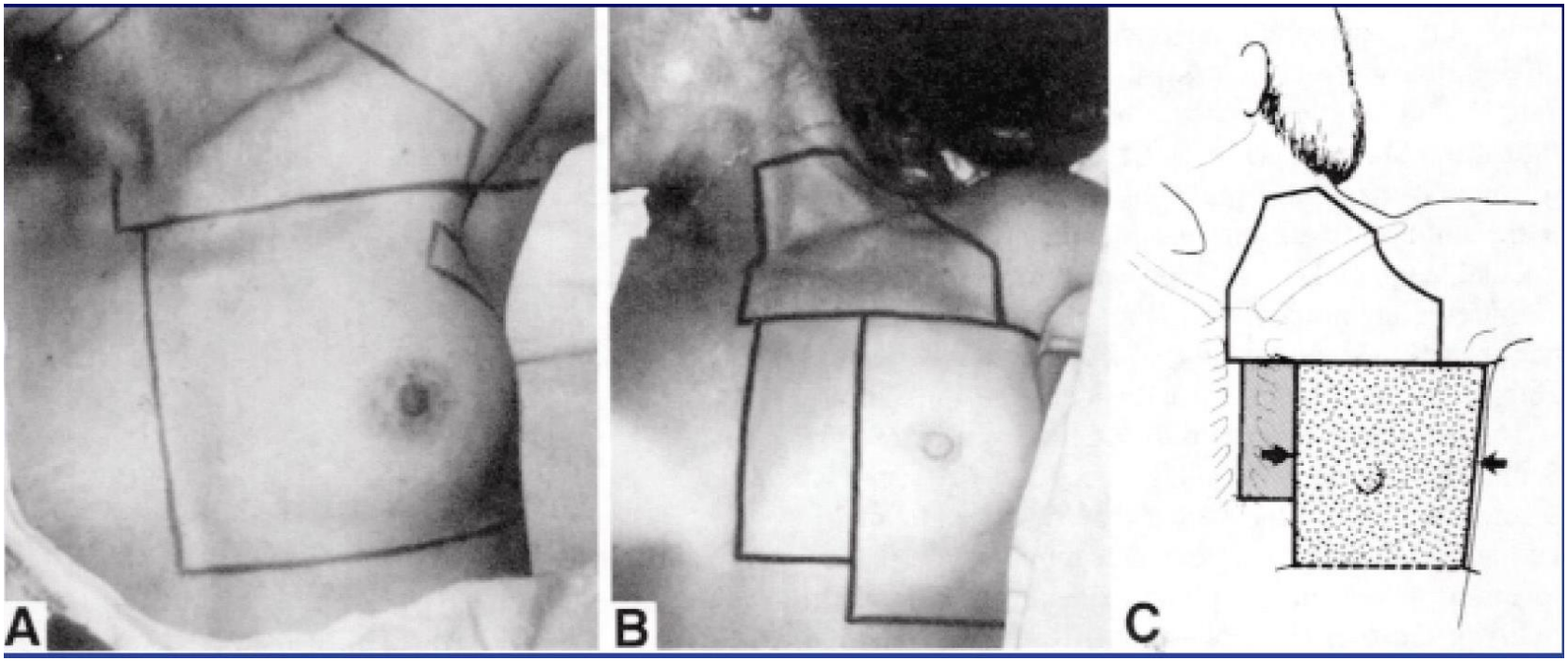
Typical breast radiation

Conventional scheme

Surgery → Chemotherapy (if any) → Radiation 5-6 wks



Typical breast radiation



Reduced radiotherapy

- Hypofractionation
- Partial breast irradiation
- Omitted RT

Objective of HypoFx

- Iso-effective to conventional fraction
  - Locoregional control
  - Cosmetic outcome
  - Same late toxicities
- Shorten treatment time
- Decrease work load and cost

Radiosensitivity of tumor

$$\text{Therapeutic ratio (TR)} = \frac{\text{Normal tissue tolerance radiation dose}}{\text{Tumor lethal radiation dose}}$$

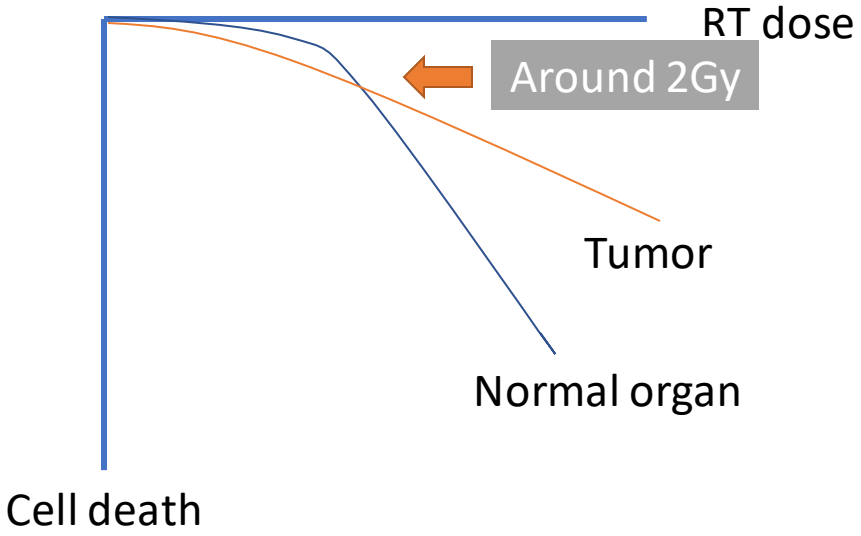
Sensitive	Intermediate		Resistant
40Gy	Relatively 60-70Gy	Relatively 70-80Gy	>80Gy
Lymphoma	Squamous cell CA	Adeno CA	Sarcoma
Germ cell			Melanoma
Small cell CA			Renal cell CA GBM

Standard dose and fractionation

Table 1 Normal tissue tolerance-linear quadratic model. What are the α/β-values (GY)?

Tissue	End point	α/β (Gy)	Range*	Reference
Early responding tissue/organ				
Skin	Erythema	8.8	6.9-11.6	(3)
	Erythema	12.3	1.8-22.8	(4)
	Desquamation		9.4-21	(5)
	Desquamation	11.2	8.5-17.6	(3)
Jejunal mucosa	Clones	13	7-13	(6)
Late responding tissue/organ				
Spinal cord	Paresis/ myelopathy	<3	1.6-5	(5)
Lung	Pneumonitis	4.0	2.2-5.8	(7)
	Pneumonitis		1.6-4.5	(5)
	Fibrosis	2.3		(5)
	Fibrosis	3.1	−0.2-8.5	(8)
Bladder	Contraction		5.8-11	(5)
Cartilage	Organ function	3.5	1-4.9	(5)
Most human	Tumors		6-25	(5)

*, 90% confidence limit (Gy) (for some of the data).



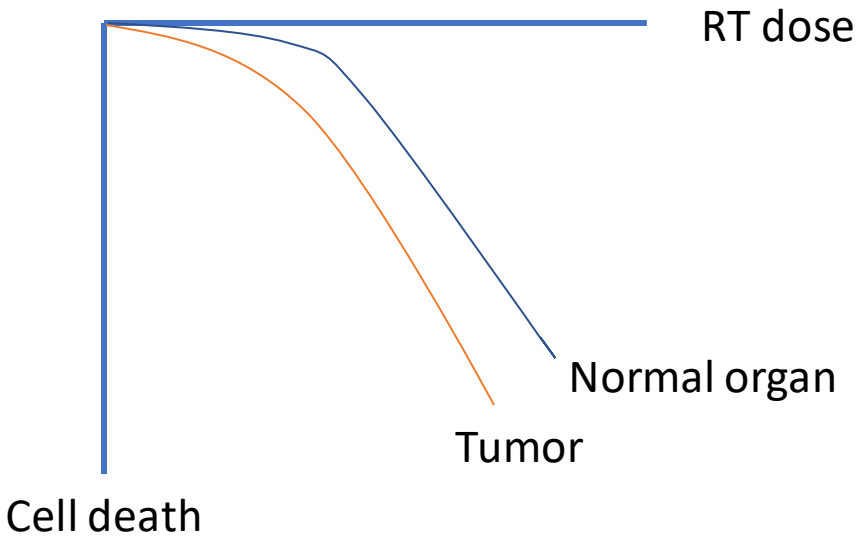


Table 2. Design and quality of randomized clinical trials

	Hôpital Necker (24)	Canada (18, 19, 21)	RMH/GOC (17, 20)	START A (10)	START B (16)
Intention to treat analysis?	–	Yes	Yes	Yes	Yes
Stratification variables	None	Age Tumor size Systemic therapy	Treatment center Margin status	Treatment center Type of surgery Intention to boost	Treatment center Type of surgery Intention to boost
Equal distribution of potential confounders	No*	Yes	–	Yes	Yes
Power	–	90% power to exclude compared to control arm.	–	80% power to detect a difference of 5% in the absolute risk of IBTR between the control and either of the experimental arms.	95% power to exclude recurrence in the experimental compared with control arm.
Percent attrition	–	0.3%	0.2%	0.2%	0.3%
Percent crossover	–	1.0%	0.1%	0.8%	0.5%
Percent non-adherentnonadherent	–	0.3%	0.7%	0.3%	0.2%
Percent lost to follow up	0%	0%	1.3%	0.4%	0.9%
Overall rating†	Poor	Good	Fair‡	Good	Good

Non inferiority

Non inferiority

Table 7. Equivalent doses in 2-Gy fractions for local-regional control of subclinical breast cancer and breast appearance for the experimental arms of the Phase III whole-breast irradiation fractionation trials

	Total dose (Gy)	Dose per fraction (Gy)	# No. fractions	Overall treatment time (days)	NTD—breast cancer (Gy)*	NTD—breast appearance (Gy)*
Conventional	50	2	25	35	50	50
Canada (18, 19, 21)	42.5	2.66	16	22	46.7†	47.7
RMH/GOC high‡ (17, 20)				35	51.4	53.2
START A high‡ (10)				35	49.2	50.8
START A low‡ (10)				35	44.9	46.2
START B (16)	40	2.67	15	21	44.0†	44.9

2.66-3.3G/F x 13-16F

Outcome of HypoFx trials

Table 5. Oncologic outcomes for randomized clinical trials comparing hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation

			Arm				IBTR		Local-regional recurrence		Disease-free survival		Overall survival	
Trial	Median Follow- up (years)	Time point for outcome reporting (years)	Dose (Gy)	# Fr	# Days	*N*	%	*p*	%	*p*	%	*p*	%	*p*
Canada (18, 19, 21)	12	10	50	25	35	612	7.5	.					84.4	
			42.5	16	22	622	7.4	<.001*					84.6	0.79
RMH/GOC (17, 20)	9.7	10	50	25	35	470	12	†						
			42.9	13	35	466	9.6	†						
			39	13	35	474	15	†						
START A (10)	5.1	5	50	25	35	749	3.2		3.6‡		86		89	
			41.6	13	35	750	3.2	0.74	3.5‡	0.86§	88	0.33§	89	0.81§
			39	13	35	737	4.6	0.40	5.2‡	0.35§	85	0.33§	89	0.99§
START B (16)	6.0	5	50	25	35	1105	3.3		3.3‡		86		89	
			40	15	21	1110	2.0	0.21	2.2‡	0.35	89	0.02	92	0.03

Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):59-68.

RT Technique in HypoFx trials

Table 3. Radiotherapy parameters for randomized clinical trials comparing hypofractionated whole breast irradiation to conventionally fractionated whole breast irradiation

	Canada (18, 19, 21)	RMH/GOC (17, 20)	START A (10)	START B (16)
Energy	Co-60, 4 MV or 6 MV	6 MV*	6 MV*	6 MV*
Wedges	Yes	Yes	Yes	Yes
Inhomogeneity cCorrections	–	GOC only	Variable	Variable
Planning	2D	2D—RMH 3D—GOC	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	–7% to +7%	–5% to +7%	–5% to +5%	–-5% to +5%
Separation	≤ 25 cm	–	–	–
Percent receiving boost	0%	75%†	61%	39%
Boost dose	–	14 Gy, 7 fr	10 Gy, 5 fr	10 Gy, 5 fr
Boost modality	–	Electrons	Electrons	Electrons
Percent receiving regional nodal irradiation				
Target for nodal irradiation				
Use of PAS				
Dose to regional nodes				

Due to concern about toxicities, trials limit maximum breast separation or homogeneity

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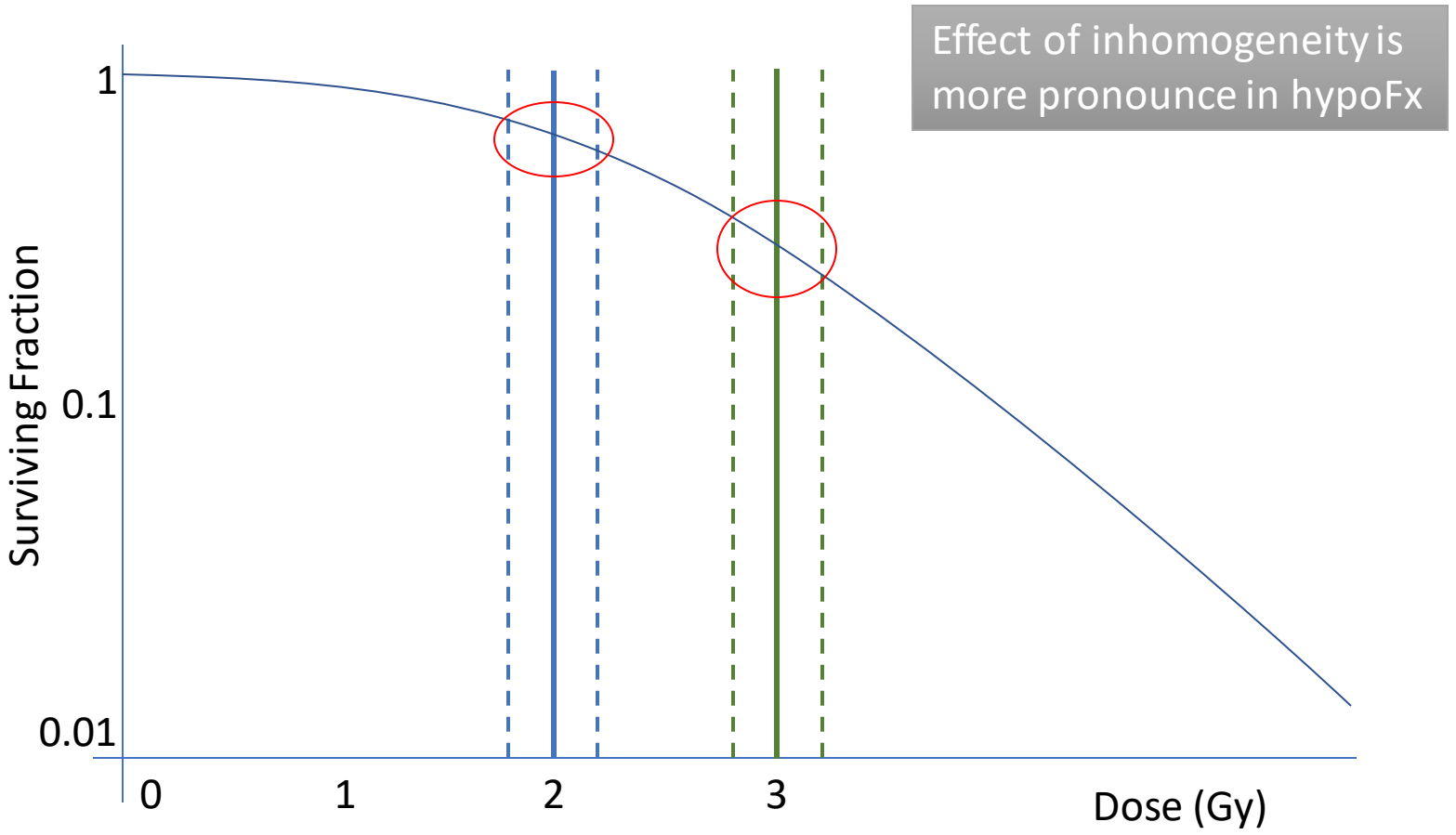
Effect of Inhomogeneity in HypoFx

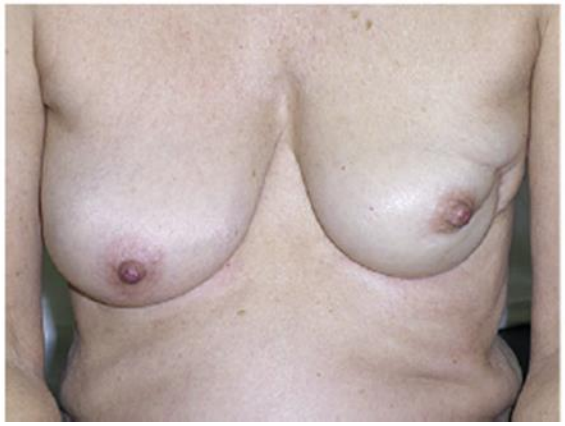
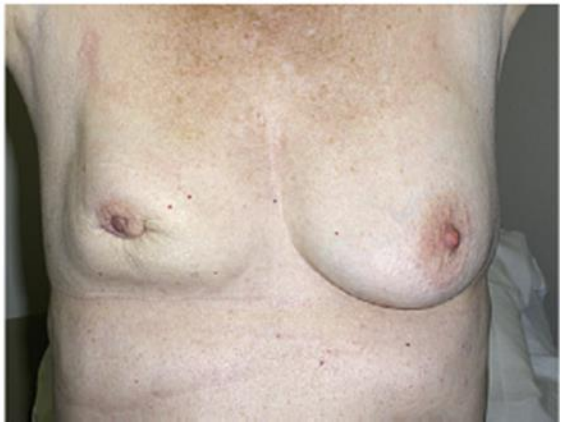
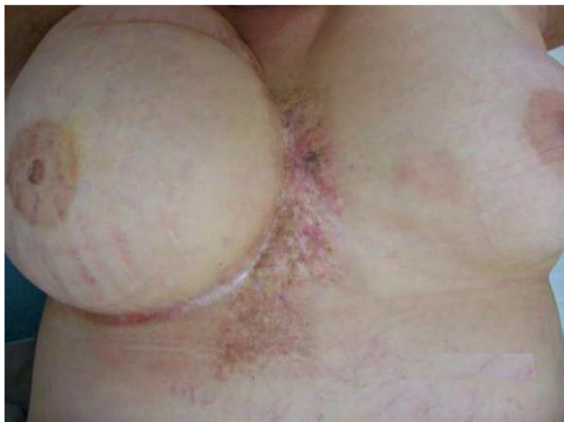


Concerned toxicities

- Cosmetic outcome
- Subcutaneous fibrosis
- Ischemic heart disease
- Pneumonitis
- Rib fractures

At 5-10 years F/U, No significant difference in toxicities

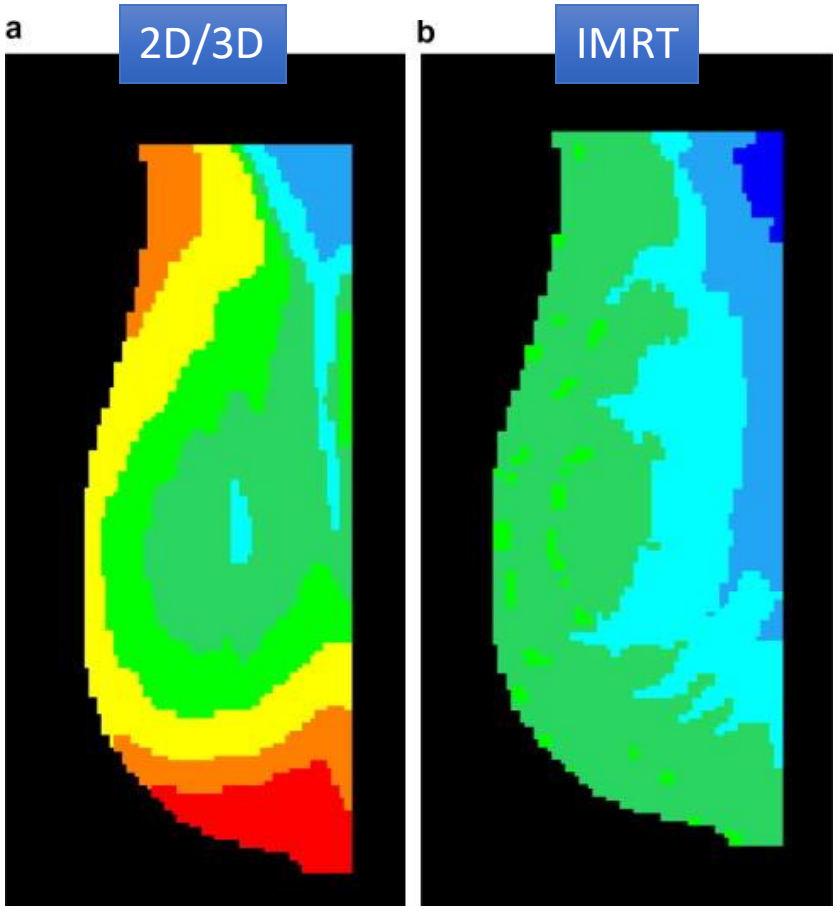
Some toxicities may need longer F/U to access

Dosimetric comparison IMRT vs 2D/3D

- IMRT significantly reduce mean volumes receiving
  - Dose >107% (10.5 vs 44.5)
  - Dose <95%(132.7 vs 180.8)

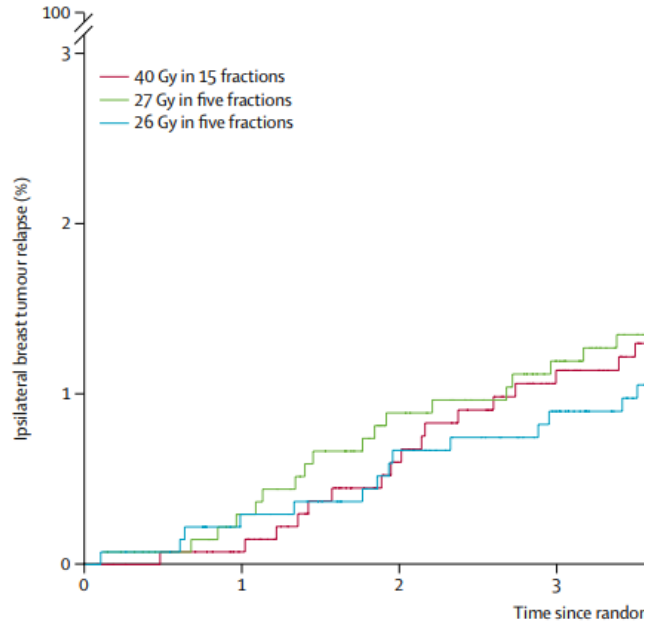
  (p<0.00005)
- IMRT also can reduce dose to other OARs (Heart, Lung)



J Med Imaging Radiat Oncol. 2009 Feb;53(1):92-9.

Radiother Oncol. 2009 Jul;92(1):34-41.

Hypofractionated breast radiotherapy 3 weeks (FAST-Forward): 5-year efficac tissue effects results from a multicentr randomised, phase 3 trial



40 Gy				
Number at risk	1361	1347	1307	1281
Censored	0	13	46	65
Events	0	1	8	15
27 Gy				
Number at risk	1367	1352	1328	1303
Censored	0	11	27	48
Events	0	4	12	16
26 Gy				
Number at risk	1368	1347	1325	1302
Censored	0	17	34	54
Events	0	4	9	12

Figure 2: **Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule**

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..
Breast distortion†	..	..	..	..	0·99 (0·95–1·02); 0·38
40 Gy	232/5724 (4·0%)	1 (ref)	..	..	..
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028	..	..
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19	0·083	..
Breast shrinkage†	..	..	..	..	1·03 (1·00–1·06); 0·023
40 Gy	330/5728 (5·8%)	1 (ref)	..	..	..
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004	..	..
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71	0·0018	..
Breast induration (tumour bed)†	..	..	..	..	1·00 (0·96–1·04); 0·95
40 Gy	185/5713 (3·2%)	1 (ref)	..	..	..
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013	..	..
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23	0·047	..
Breast induration (outside tumour bed)†	..	..	..	..	0·96 (0·90–1·02); 0·17
40 Gy	45/5712 (0·8%)	1 (ref)	..	..	..
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001	..	..
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013	0·059	..
Telangiectasia	..	..	..	..	1·21 (1·14–1·29); <0·0001
40 Gy	63/6087 (1·0%)	1 (ref)	..	..	..
27 Gy	100/6272 (1·6%)	1·68 (1·07–2·65)	0·025	..	..
26 Gy	102/6300 (1·6%)	1·53 (0·96–2·43)	0·070	0·65	
Breast or chest wall oedema	..	..	..	..	0·73 (0·69–0·78); <0·0001
40 Gy	89/6097 (1·5%)	1 (ref)	..	..	..
27 Gy	217/6287 (3·4%)	2·18 (1·57–3·03)	<0·0001	..	..
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032	0·0097	..
Breast or chest wall discomfort	..	..	..	..	0·93 (0·89–0·97); 0·0003
40 Gy	234/6086 (3·8%)	1 (ref)	..	..	..
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44	..	..
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86	0·35	..

Results for years of follow-up show trend in normal tissue effects over follow-up across all fractionation schedules. p values are calculated by Wald test; odds ratios are estimated from the generalised estimating equations model including all follow-up data and show relative odds of moderate or marked adverse event (vs none or mild) for each pairwise comparison of fractionation schedules across all follow-up assessments. *Includes shrinkage, induration, telangiectasia, or oedema. †Patients who had breast conservation surgery or mastectomy with reconstruction.

Table 4: **Longitudinal analysis of moderate or marked clinician-assessed late normal tissue effects for patients with at least one annual clinical assessment (n=3975)**

AM Brunt., Lancet. 2020 May 23;395(10237):1613-1626.

Breast RT Fractionation

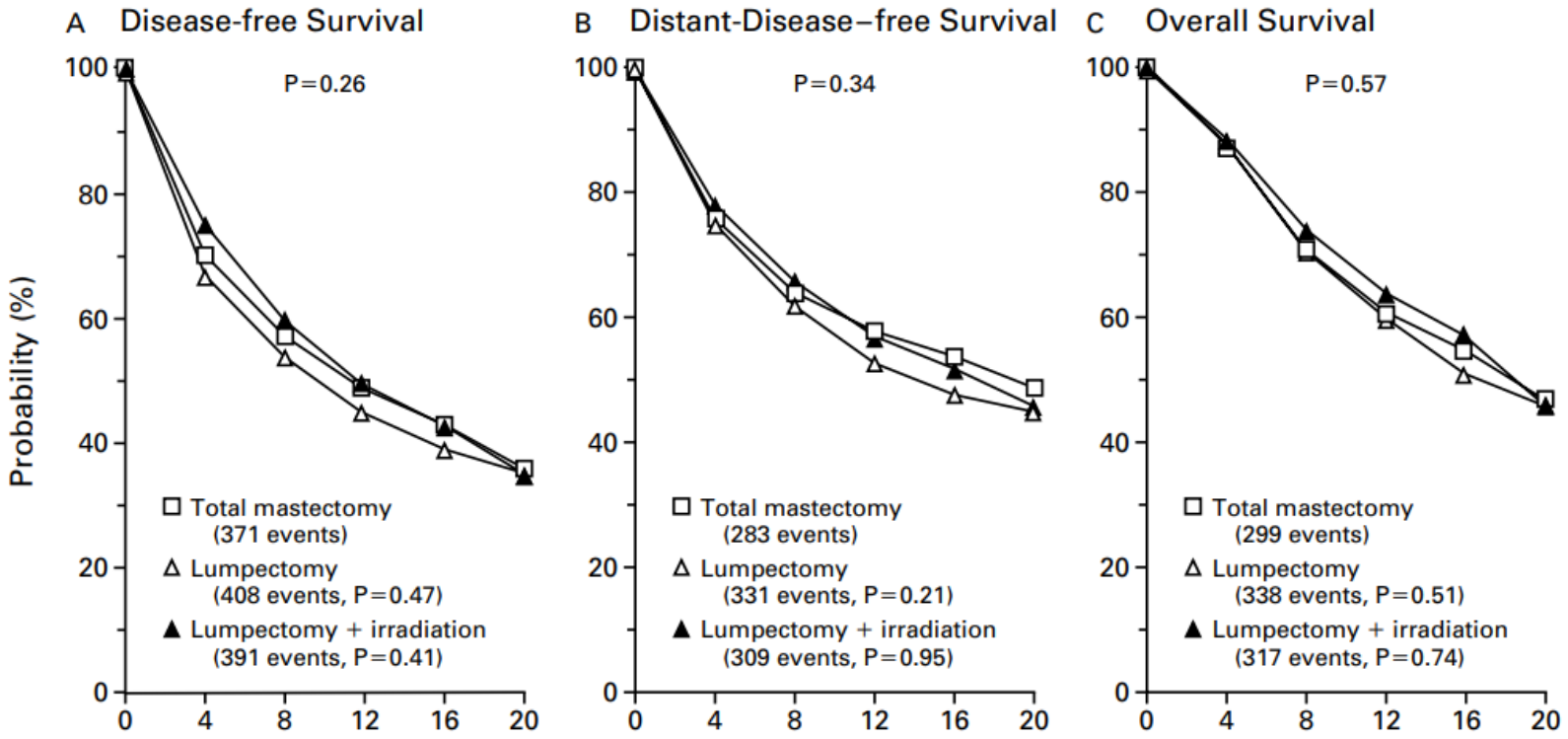
Duration	Dose (Gy)	Dose/F	BED (Gy3)	BCS	PMRT	RNI
5 Weeks	50	2	78.5	✓✓	✓✓	✓✓
				- Standard of care for long time		
3 Weeks	42.5	2.67	74.9	✓✓	✓	✓
				- Popular hypofractionation regimen and now accepted as standard of care - No difference in outcomes and complications		
1 Week	26	5.2	64.6	✓	✓	Ongoing
				- Push the boundary for hypofractionation - Follow up is quite short (5 Yrs) - Slightly worse cosmetic effects		

Reduced radiotherapy

- Hypofractionation
- Partial breast irradiation
- Omitted RT

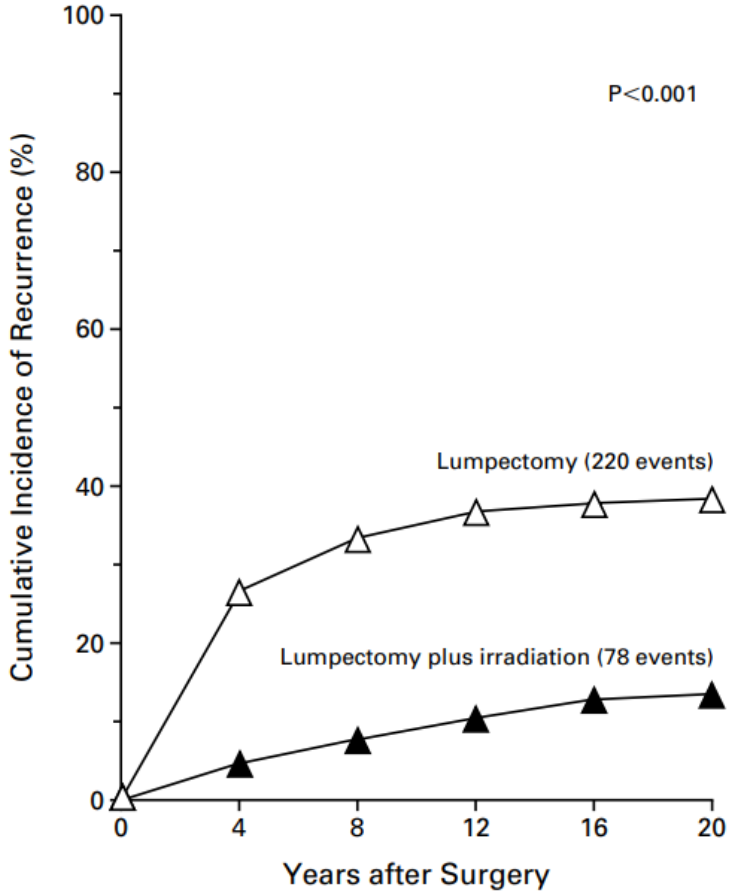
For early stage, after breast conserving surgery
- Do we really need to irradiate to WHOLE breast?
- Do we really need to irradiate?

Mastectomy vs BCS vs BCS+RT



NSABP-B06, RCT 2163 pts between 1976-1984

Mastectomy vs BCS vs BCS+RT



- NSABP-B06 results
  - No OS difference
  - Lumpectomy alone has higher recurrence than lumpectomy + RT
  - 20yrs incidence of ipsilateral recurrence were 14.3 vs 39.2%

NSABP-B06, RCT 2163 pts between 1976-1984

Radiation after BCS

- Meta-analysis showed that adjuvant RT reduced recurrence around 16% at 10 years and avoid breast cancer death by 4% at 15 years (4 : 1)

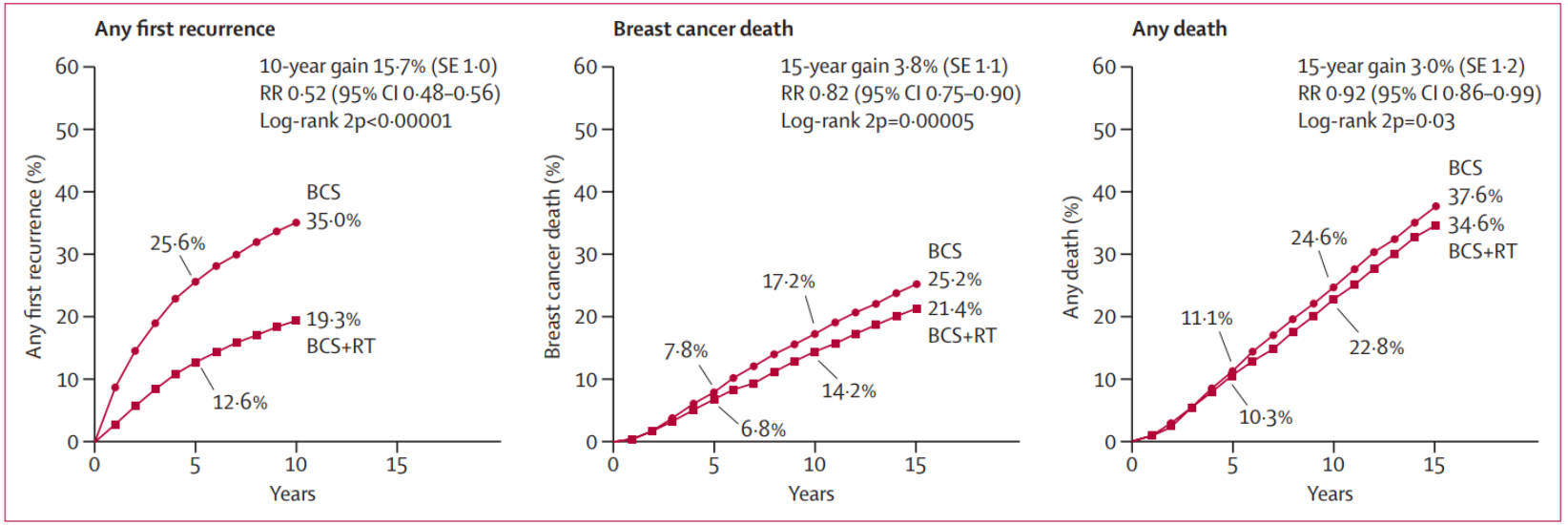
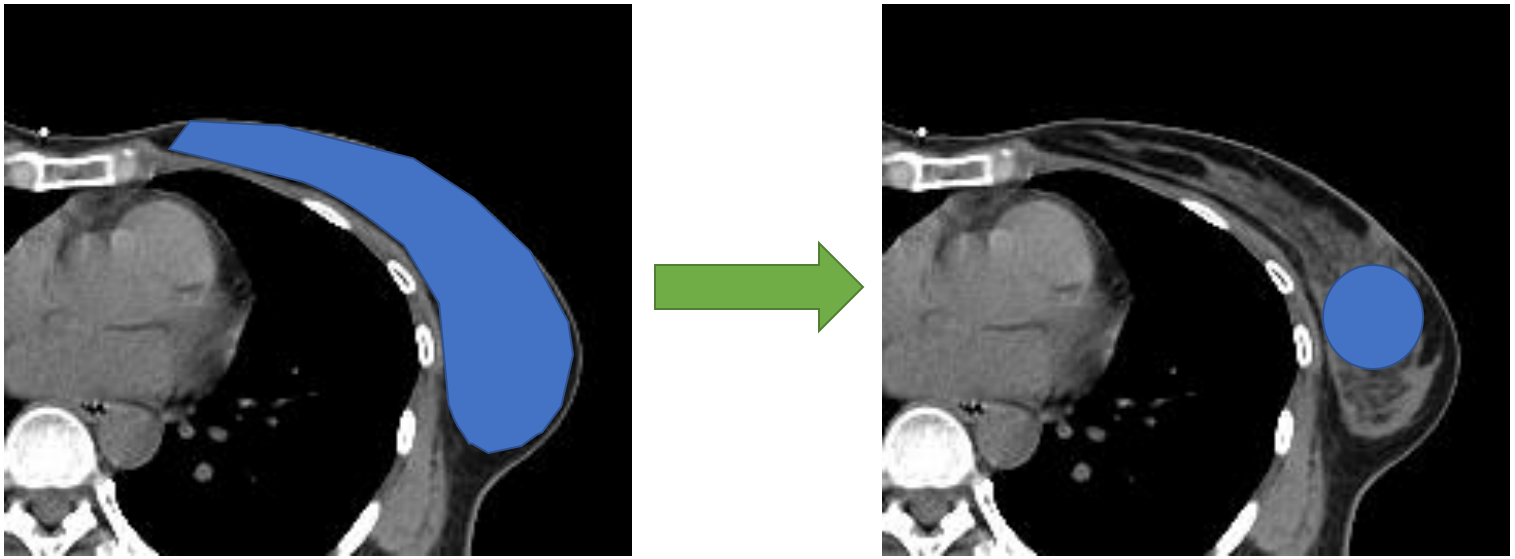


***Figure 1*: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials**
Further details are in webappendix p 5. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

EBCTCG, Lancet 2011

Rationales for APBI

- Clinicopathological paradox
  - Two-thirds of specimens of mastectomies harbor occult cancer foci distributed throughout the breast
  - Most local recurrences in the conserved breast appear in the original tumor bed



Comparison of APBI technique

Table 5
Comparison of PBI techniques

	3D CRT	Interstitial brachytherapy HDR, LDR, PDR	MammoSite	Targit, 50 kV X-rays	IORT, electrons
Coverage of target Thickness of cavity wall irradiated	Best PTV = tumor bed + 20–25 mm. Often 5 mm to field edge from PTV	Variable 1–2 cm	Good Dose prescribed to 1 cm from surface of applicator	Good Dose prescribed to 1 mm from surface of applicator. 5–7 Gy 10 mm from applicator	Good Dose prescribed to 90% isodose line. 80% isodose a 13 mm (3 MeV)–24 mm (9 MeV)
Dose homogeneity	Best	Fair	Fair	Fair	Fair
Sparing of normal breast / other organs	Least	Good	Good	Best	Varies with location
Skin dose	Least			Least (	
Technical feasibility for various size, shape or location of cavity	Suitable f all cases	/irregular iphery of near axilla	the breast	Not su irregu periphery of the breast	ors /axilla or skin
Expertise required	Average	High	Average	High	Very high
Potential for wide spread use	Very good	Fair	Very good	Fair	Limited
Main drawback	Relatively higher dose to normal tissue and breathing motion	Adequacy of target coverage in some cases and wider applicability	Cavity shape and size. Although easy to use, stringent QA is required. Skin dose may be high	Very limited depth irradiated; cavity shape and size. Histology not available	Wider applicability. Histology not available. Based on quadrantectomy

Modified from Sarin [113].

Fractionated, after surgery
Usually 34-38.5Gy/10Fx in 5 days

1 Fx, at time of surgery
Usually 20-21Gy

Radiotherapy and Oncology 90 (2009) 1–13

External Beam Radiation (3D)

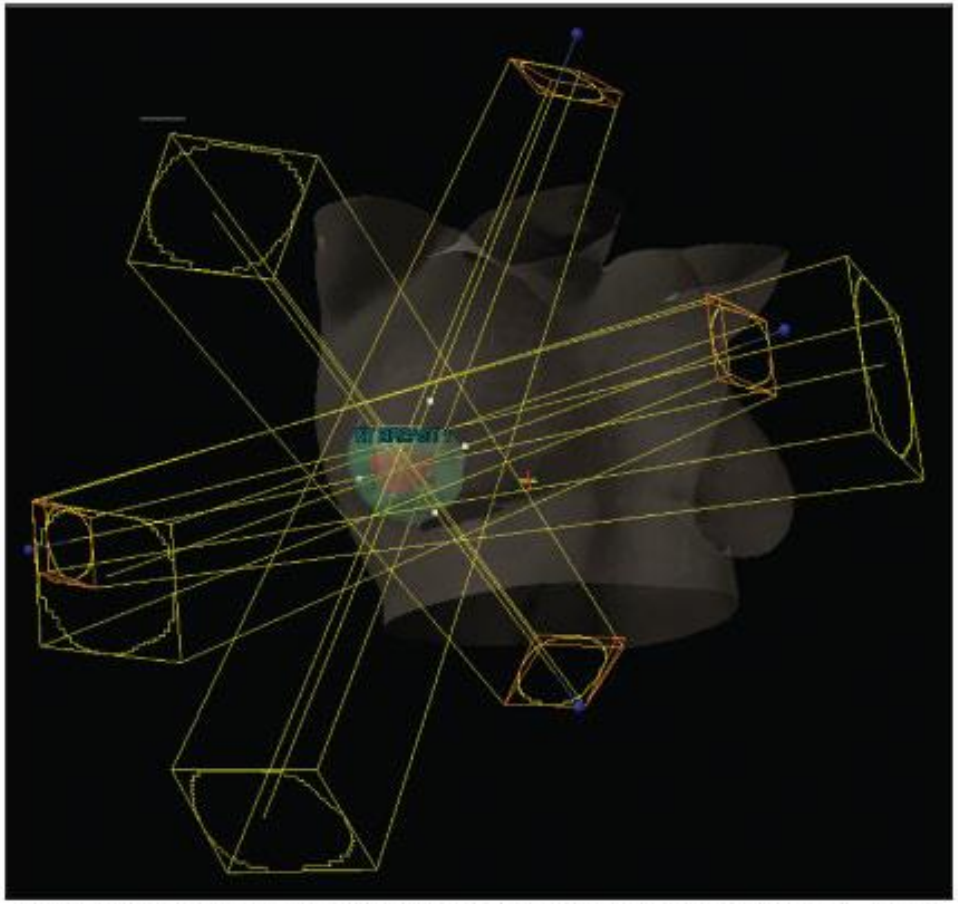


Figure 3: Three-Dimensional Conformal Radiation Therapy—This noninvasive method of delivering accelerated partial-breast irradiation provides increased dose homogeneity, leading to the theoretical potential for better cosmetic outcomes compared to other techniques.

Brachytherapy – MammoSite

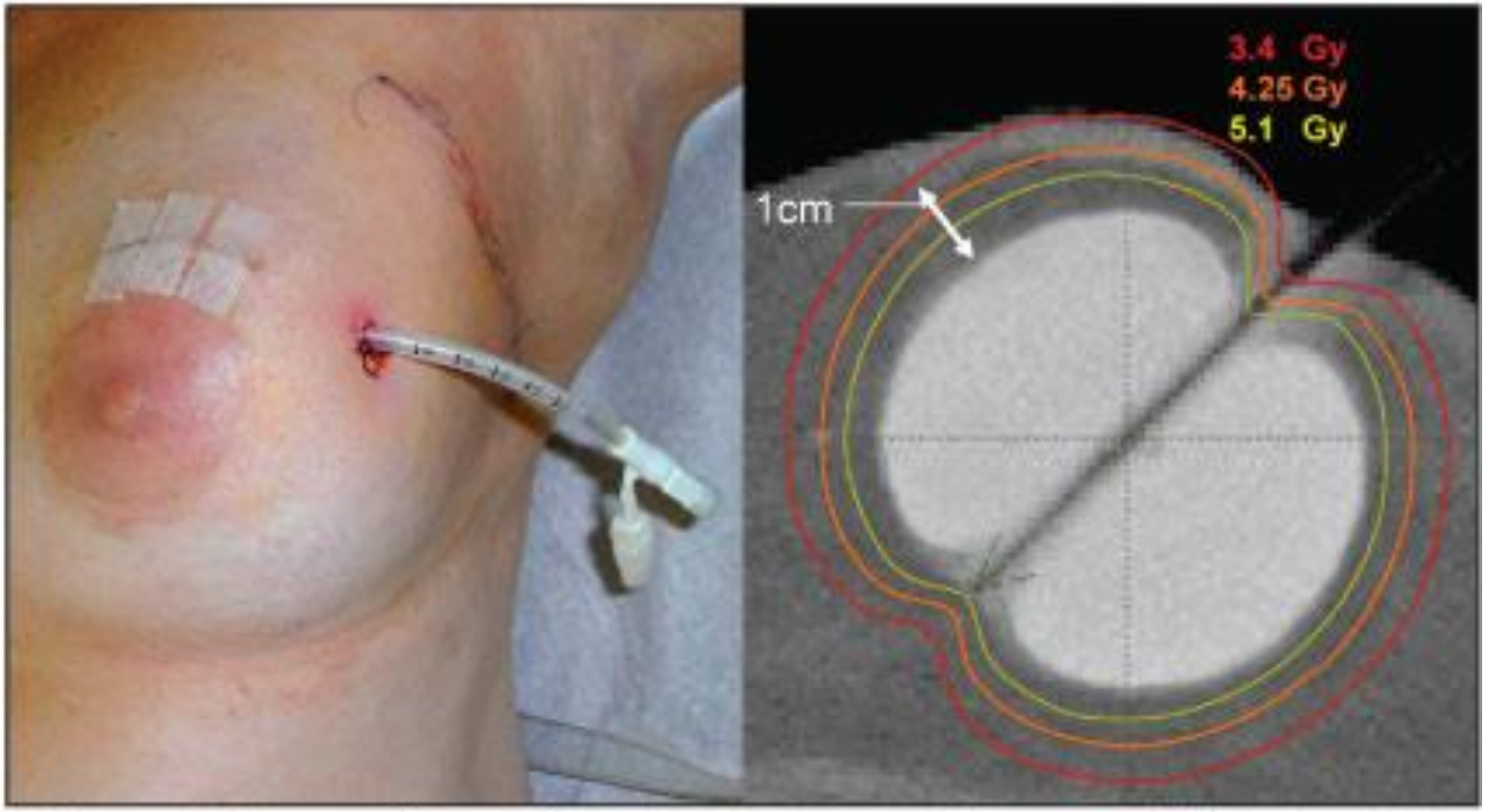
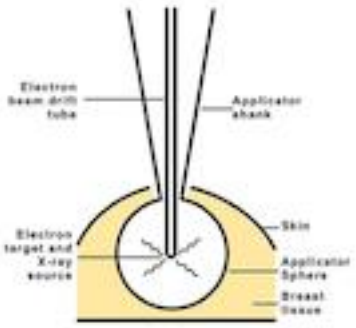
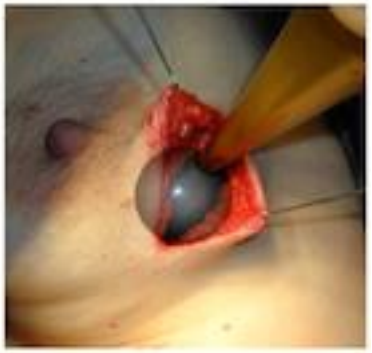


Figure 2: MammoSite Balloon Brachytherapy—External (left) and sagittal (right) views of balloon with dosimetric target coverage. Photographs courtesy of Douglas Arthur, with permission from the *Journal of Clinical Oncology*.

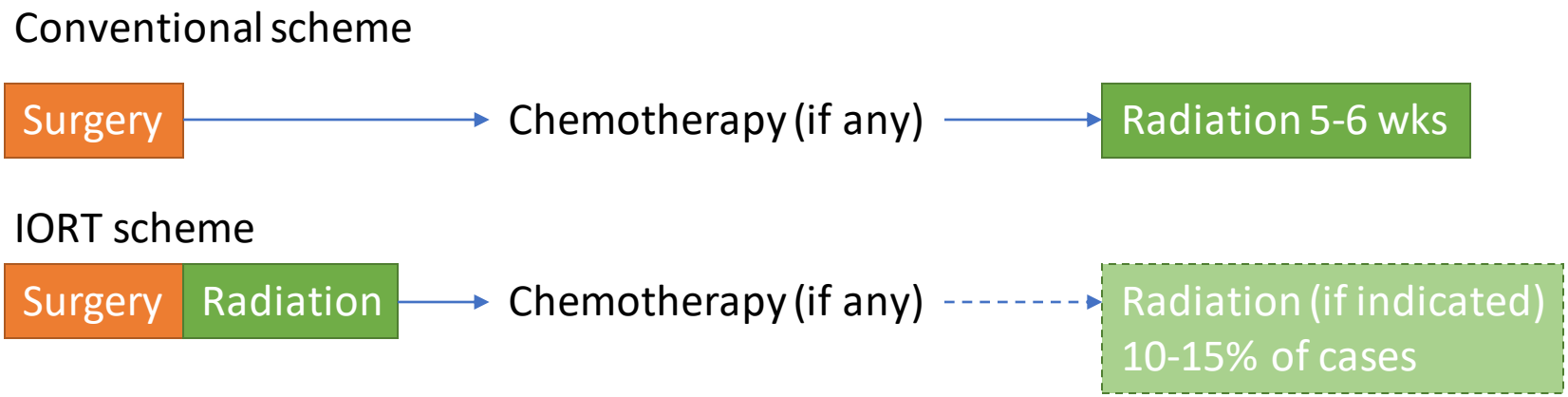
INTRABEAM :: TARGIT

- TARGIT (TARGeted Intra-operative radioTherapy)
- Mobile X-ray source which emits low energy X-ray radiation (max. 50 kV) in isotropic distribution





Conventional vs IORT



- IORT (with TARGIT in selected patients) showed ,at least, non inferior to whole breast radiation in term of local control and survival
- There still have some doubts to be answer
  - Complication of IORT and what if IORT+EBRT
  - Can we do a wider surgery to avoid IORT
  - Can patients suitable for IORT be safely omit radiation

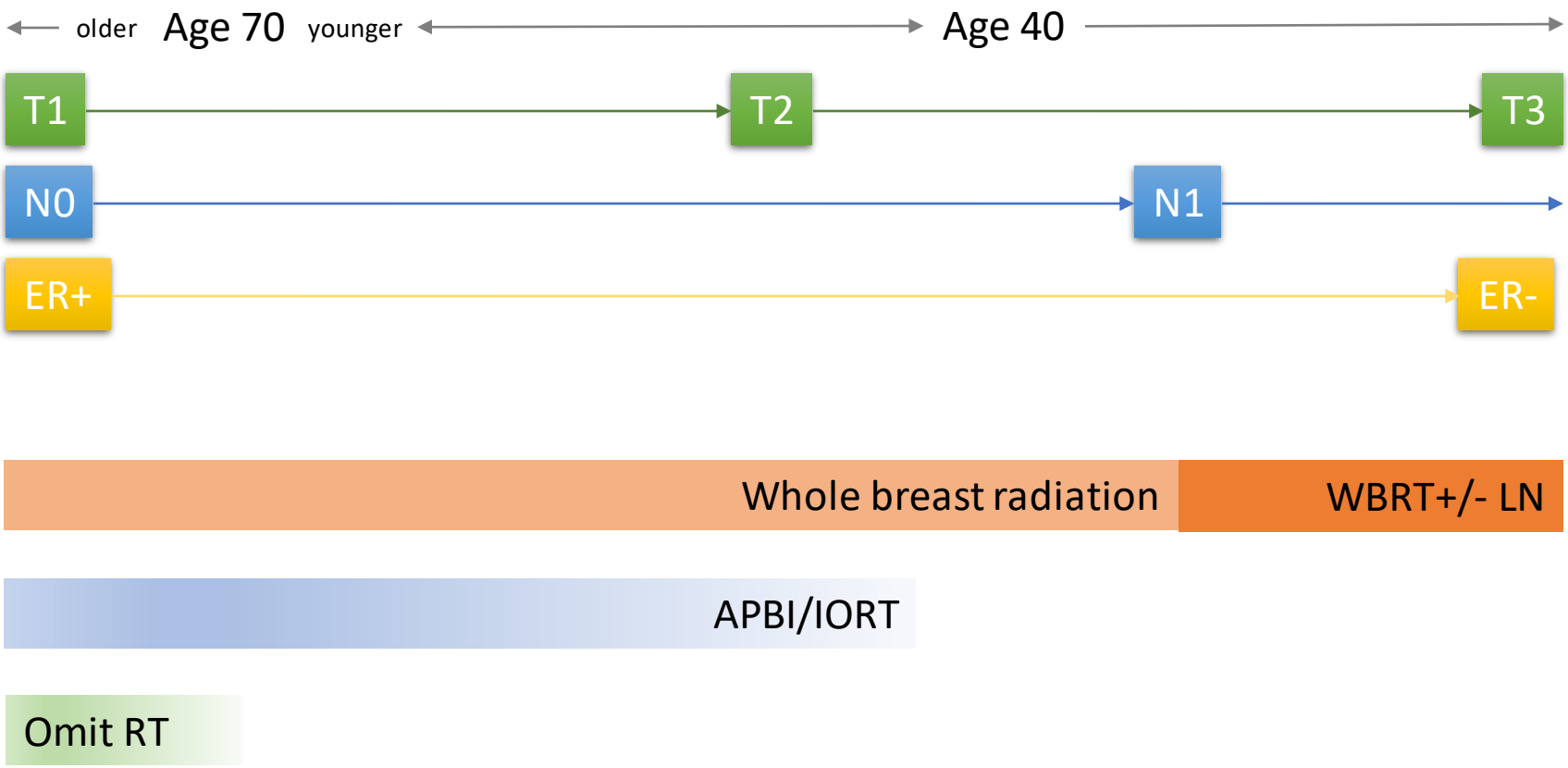
Omitted RT in elderly

- May consider to omit RT in low-risk elderly group
  - Low recurrence rate
  - Avoid long 5-6 weeks of radiotherapy
- Data mainly from
  - CALGB C9343 (>70 yrs, T1N0, ER+)
  - PRIME II (>65 yrs, T1-2(<3cm)N0, ER+)
- RT improve LRR 4% -> 1%, but no different in OS

IORT vs Omitted RT

- No published direct comparison between IORT and omitted RT
- Overall survival was not difference in low or very low risk patients
- RT still has local control benefit but absolute is small enough to omit
  - However, LRR rate were usually >= 10%
  - Except those age >70 and ER+

RT options for early breast cancer



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				- Popular hypofractionation regimen and now accepted as standard of care - No difference in outcomes and complications		
1 Week	26	5.2	64.6	✓	✓	Ongoing
				- Push the boundary for hypofractionation - Follow up is quite short (5 Yrs) - Slightly worse cosmetic effects		