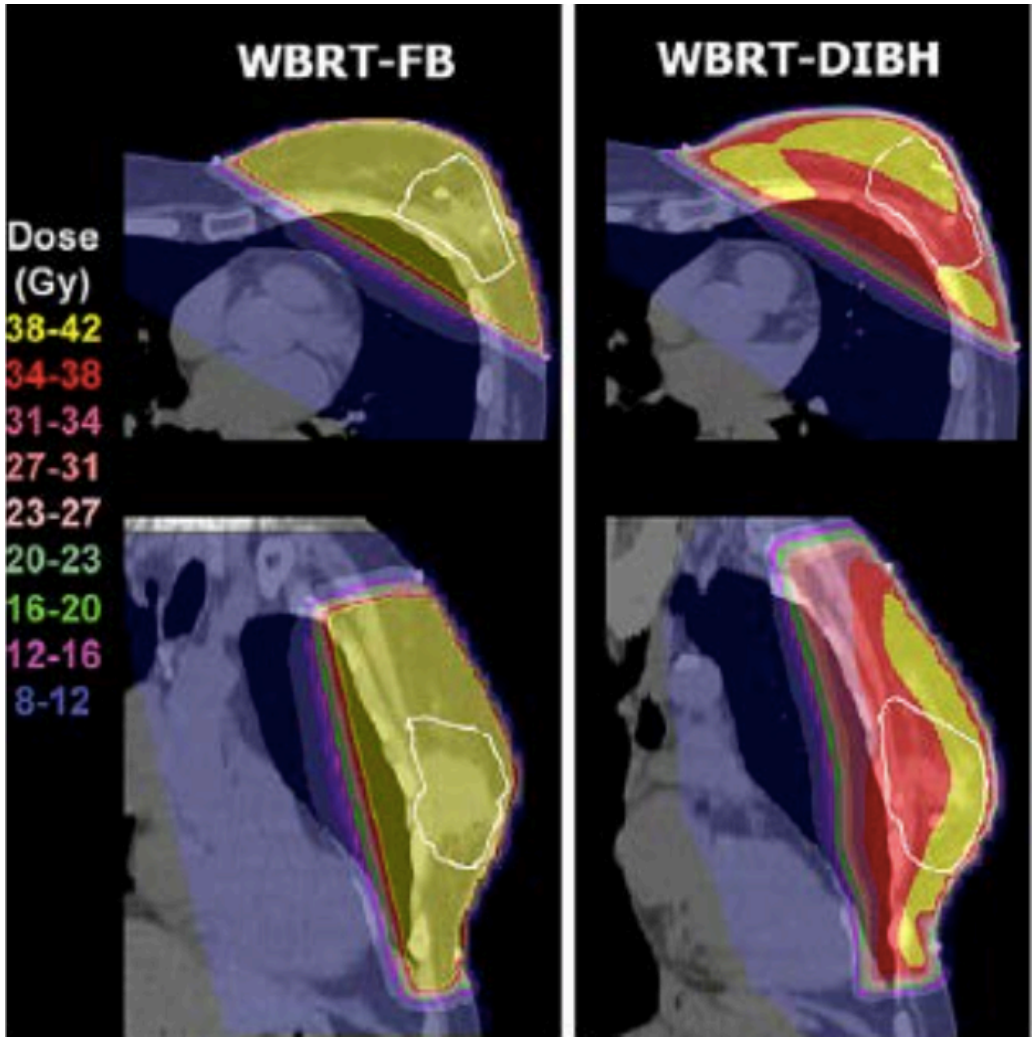
Fast Forward Breast Radiotherapy: From 5 Weeks to Only 1



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Asian American
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Intro

- In 2008, a UK Trial showed that a 3 week course of hypofractionated RT was equivalent to the conventional 5 week course for adjuvant treatment of the breast which had been in use for the past 3 decades.

- It would take another 10 years for the 3 week course to be accepted as the International Standard

- In Apr 2020, a timely article on shortening Breast Radiotherapy from 3 weeks to 1 week was published by the same UK Group in the Lancet

- While 3 weeks was already an abbreviation vs 5 weeks, somehow, some patients still view RT as a 'high (psychological) barrier'

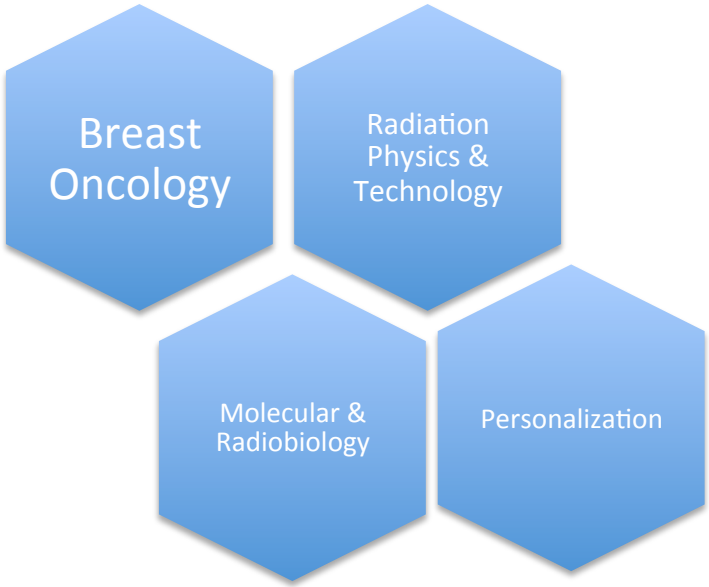
- More pertinent to the times is the potential for reduced exposure and patient caseload during the Covid-19 pandemic

Intro

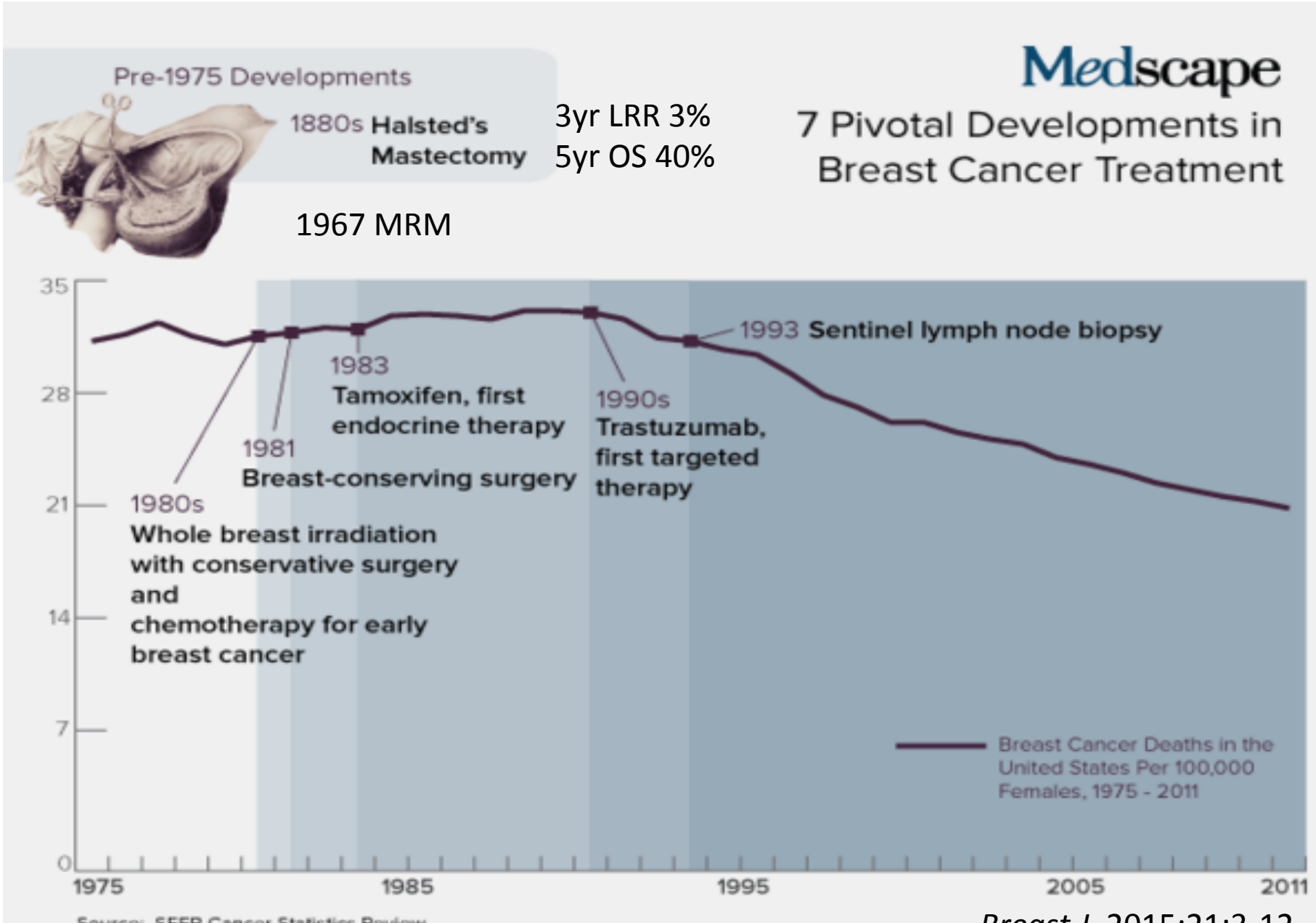
- This Talk is to update everyone of this ‘New’ Possibility in our clinic
- In so doing, take us on a walk through a brief history of Local Rx for Breast Cancer
- The focus will be on general & clinical concepts (although there’s lots more biological, statistical and technical details recorded in the actual paper)
- With the buzz surrounding molecular biology, I also hope to show how my techie colleagues and I spend our daily grind fiddling with technology to deliver better outcomes for our patients ☺

Scope

- Evolution of Local Therapy of Breast Cancer
- Concept and Results of the Lancet Paper
- Clinical Adoption and Application
- Future Directions and Conclusion



Evolution of Local Therapy of Breast Cancer



Breast J. 2015;21:3-12

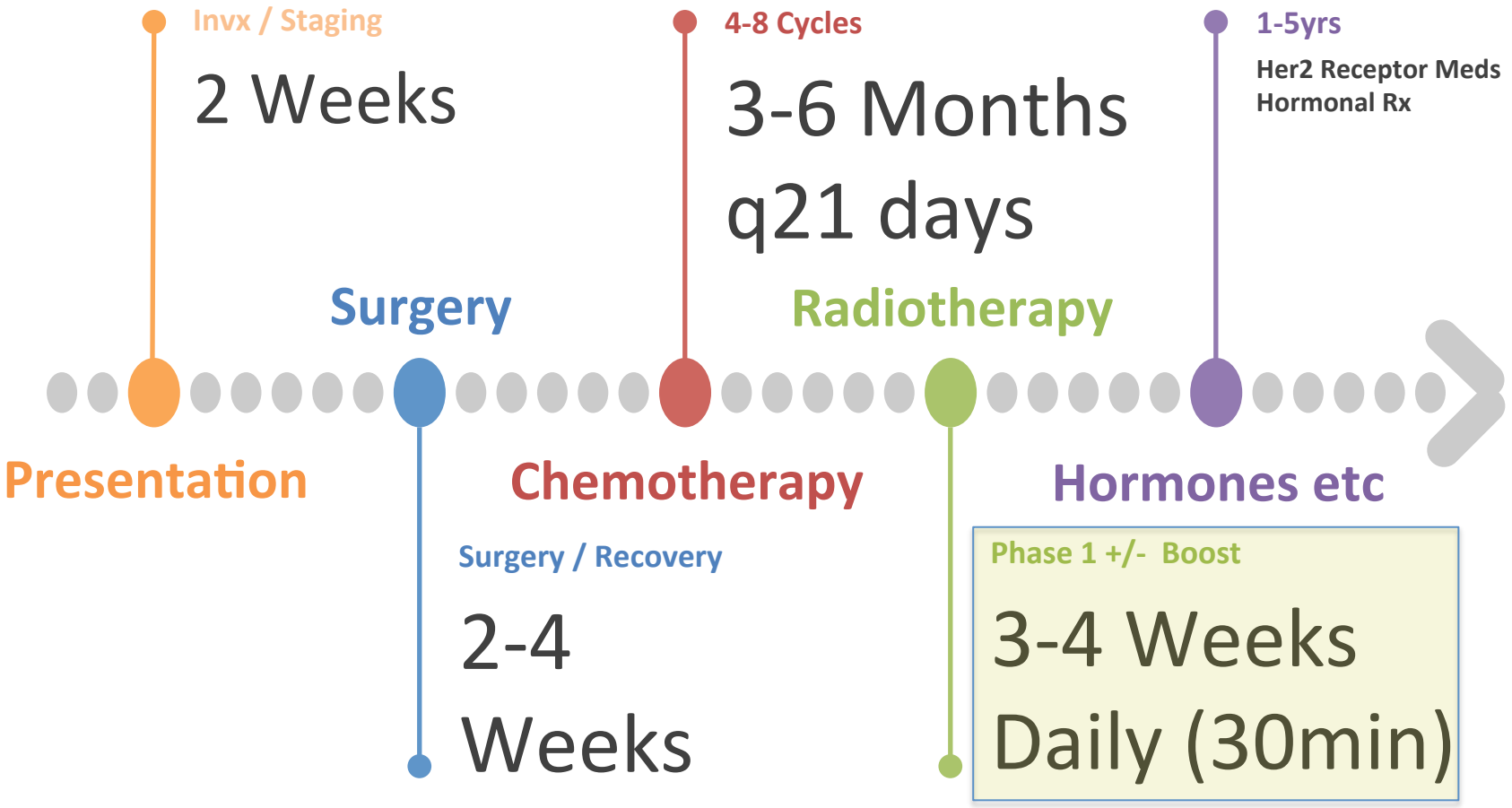
Table. Other Significant Treatment Developments

Year	Milestone
1971	The first clinical study of tamoxifen shows that it can induce temporary remission in late breast cancer
1985	A randomized trial comparing lumpectomy with mastectomy shows that disease-free and overall survival are no worse with less radical surgery
1990	The omission of radiotherapy (RT) in breast cancer patients is shown to result in high recurrence rates but has no effect on survival
1998	A meta-analysis shows that tamoxifen significantly reduces recurrence and mortality in pre- and postmenopausal women with estrogen-receptor-positive cancers, and that the longer the treatment (up to 5 years), the greater the effect
	The *HER2*/neu oncogene is established as a prognostic factor, a predictive factor, and a target for therapy
2001	A RT boost to the tumor bed after whole-breast radiation shows significant benefit in terms of recurrence for the first time in a randomized controlled clinical trial (sponsored by the European Organization for Research and Treatment of Cancer)

2003	The first randomized clinical trial (conducted at the European Institute of Oncology) comparing SNB with axillary dissection in breast cancer shows no difference in recurrence, distant metastasis, or survival
2005	The major HERA trial shows that trastuzumab should be administered for 1 year as standard treatment for *HER2*-positive disease
2008	Hypofractionated RT (40 Gy given over 3 weeks) is shown to be equivalent (in recurrence rate and late toxicities) to conventional fractionation
2011	A large meta-analysis shows that RT reduces breast cancer mortality
	The ACSOG Z011 trial shows that axillary dissection can be safely omitted in postmenopausal women, even if 1 or 2 sentinel nodes are positive (most patients in the trial received systemic therapy and whole-breast radiation)

2012	Ten years of adjuvant treatment with tamoxifen is shown to be significantly better than the standard 5 years in terms of reducing the risk for breast cancer recurrence and disease-specific death in the randomized controlled ATLAS trial
	The first evidence that IMRT can reduce acute toxicity, compared with standard 2-dimensional RT, is published
2013	The five major subtypes of breast cancer — luminal A, luminal B, luminal B-like, *HER2*-positive, and triple-negative — are established
2014	An algorithm is established for the treatment of premenopausal, hormone-receptor-positive early breast cancer, and the SOFT and TEXT trials show that adjuvant treatment with the aromatase inhibitor exemestane plus ovarian suppression is associated with significantly fewer recurrences than tamoxifen plus ovarian suppression for 5 years.
	The addition of pertuzumab to trastuzumab and docetaxel improves median overall survival by 15.7 months in the major CLEOPATRA clinical trial

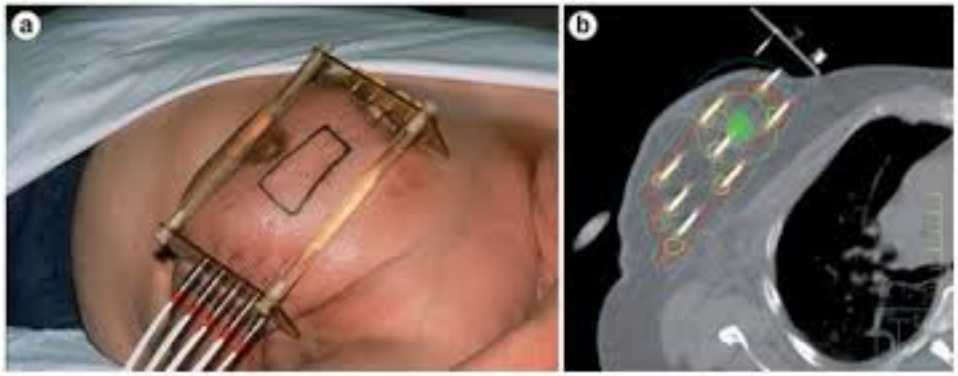
6-9 Month Treatment Course From Diagnosis to End of RT



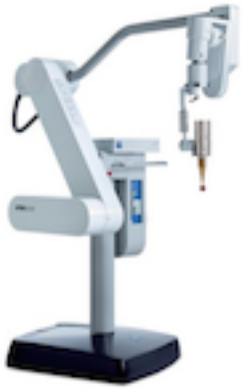
Evolution of Local Therapy of Breast Cancer

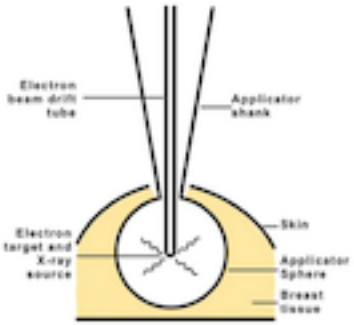
- Quest for: Improved Survival, Reduced Toxicity
- Since early 2000s many attempts were made to Minimize Downtime

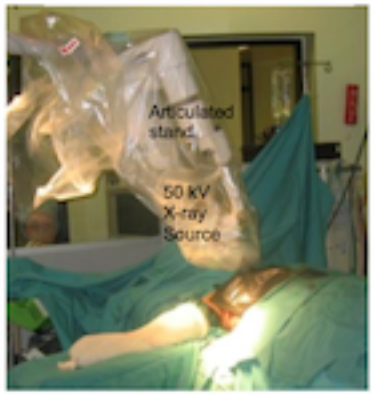
- APBI- Accelerated Partial Breast RT
- Strict Selection Criteria
- Complex Logistics, Cost etc

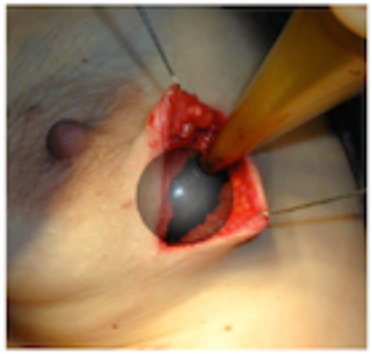


Brachytherapy (8-10 sessions over 4-5 days)









IORT – Intra-operative RT (~30min Intra-op)

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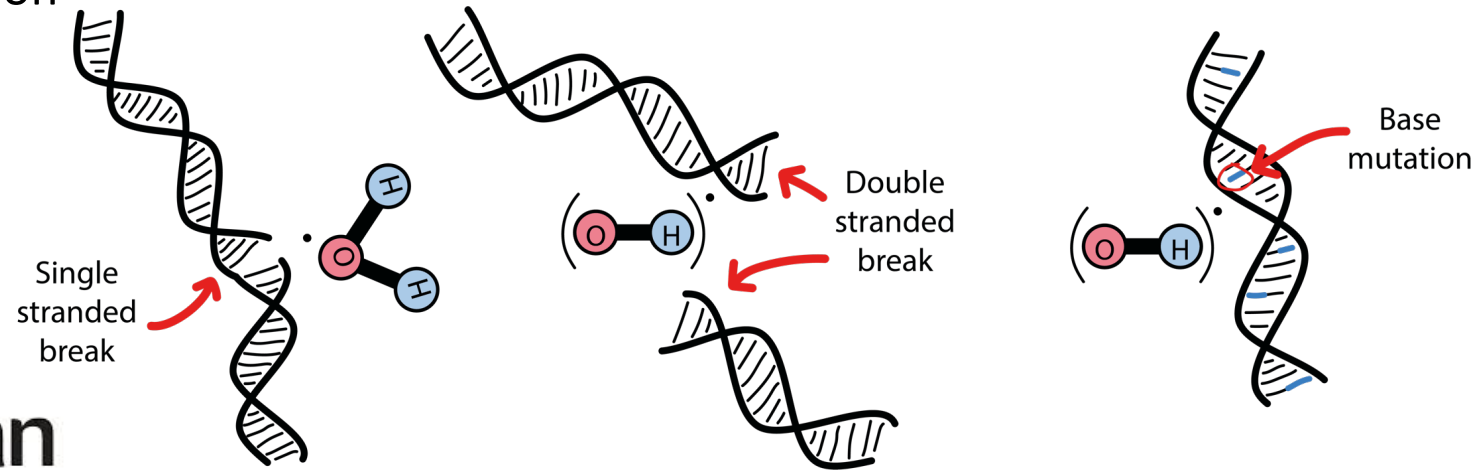
Harnessing Technology . Enabling Hope

A Word about the Concept of Radiotherapy

- Small Packets of Energy delivered by Ionising Radiation to cause damage to DNA of replicating cells

- Geometrical Modifications influence how the energy is deposited and hence how the damage is distributed

- Biological Strategies focus on leveraging **therapeutic window** based on intrinsic **Radio-sensitivity** of different targets by varying the Packets / Intensity of the Radiation



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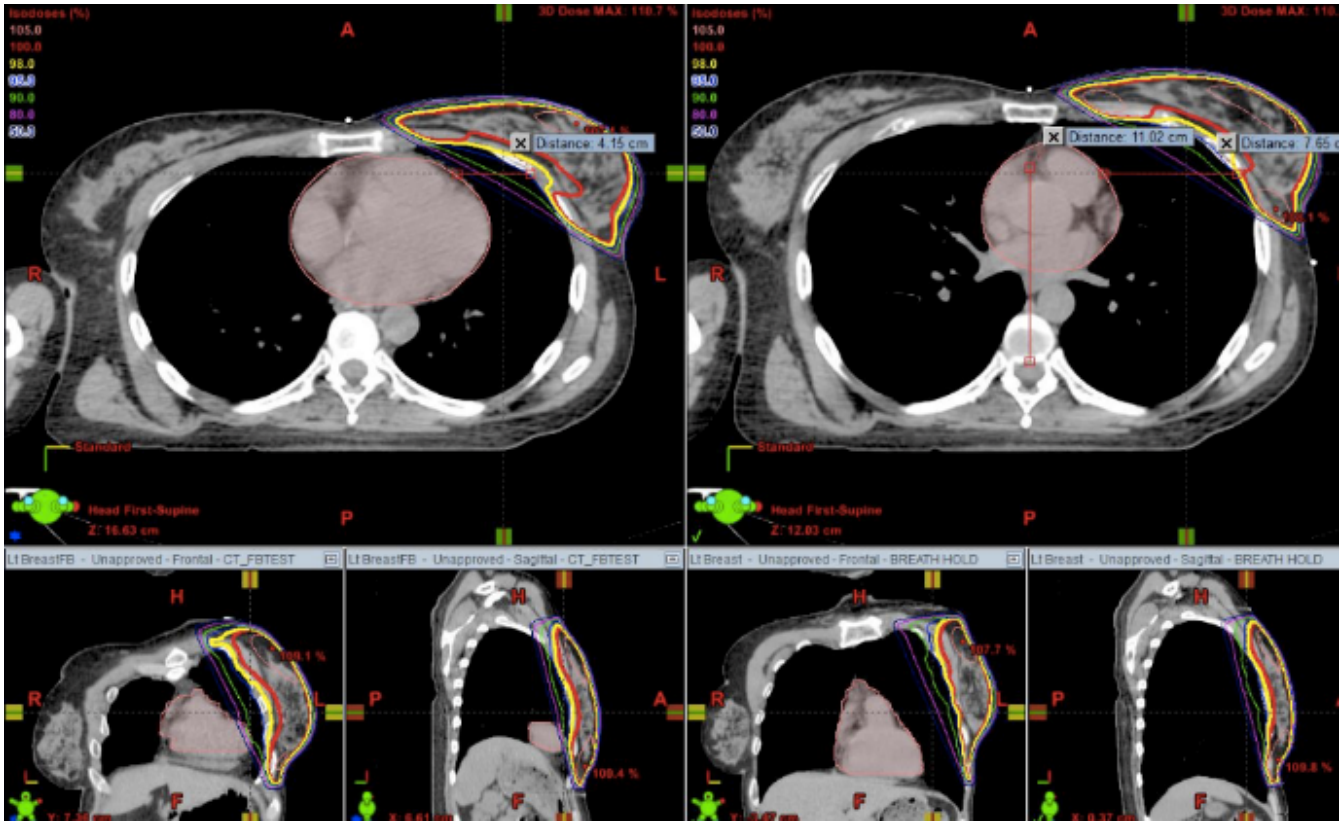
Evolution of Local Therapy of Breast Cancer

Avoid RT toxicities:

- Deep-inspiratory Breath Hold



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Harnessing Technology . Enabling Hope

Evolution of Local Therapy of Breast Cancer

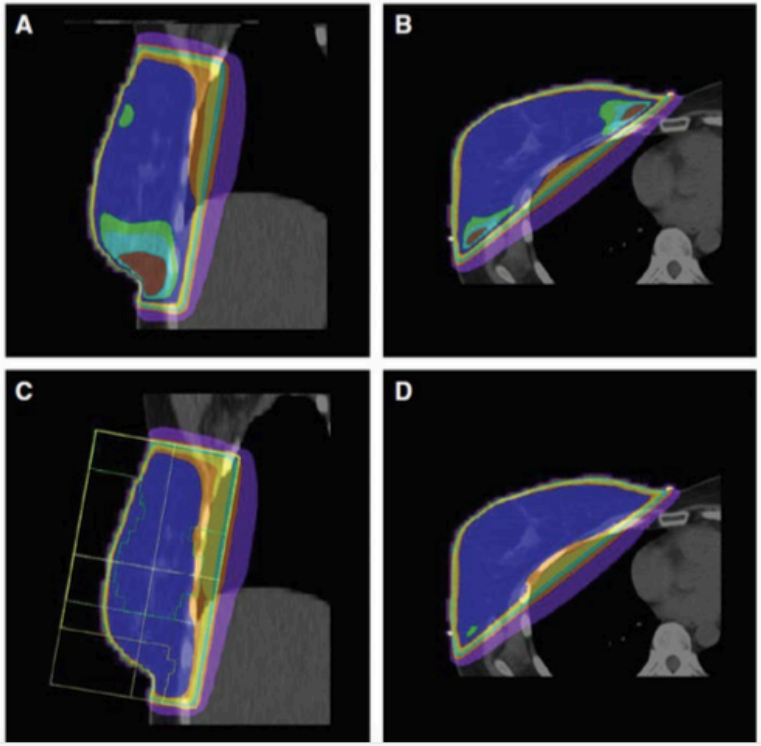
VOLUME 31 · NUMBER 36 · DECEMBER 20 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Controlled Trial of Intensity-Modulated Radiotherapy for Early Breast Cancer: 5-Year Results Confirm Superior Overall Cosmesis

Mukesh B. Mukesh, Gillian C. Barnett, Jennifer S. Wilkinson, Anne M. Moody, Charles Wilson, Leila Dorling, Charleen Chan Wah Hak, Wendi Qian, Nicola Twyman, Neil G. Burnet, Gordon C. Wishart, and Charlotte E. Coles

Avoid RT toxicities:

- Intensity Modulation (Field-in-Field technique)



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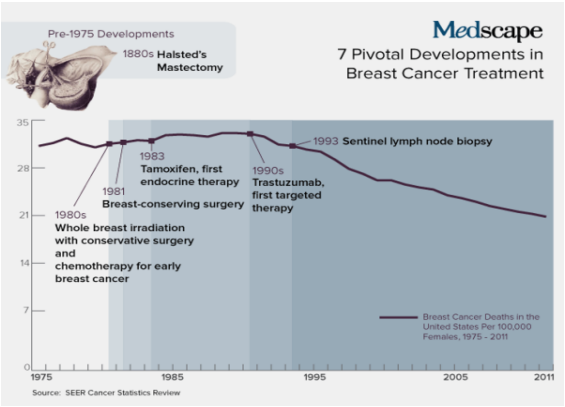
Evolution of Local Therapy of Breast Cancer

- Shorter Treatment Time requires High Doses per fraction
- Safe Delivery of High Dose Fractionation Schemes are aided by Technological Advances in Treatment Planning and Delivery
- The Stage has already been set …

Evolution of Local Therapy of Breast Cancer

- ‘Breast Cancer is a surgical disease’
- Greatest Cure when early detection and effective local treatment is administered
- Probably Most Cost Effective too!
- Combined w Population-Based Screening



- Minimally-invasive Procedures + Minimum Time / Toxicity > > Potential to Improve Compliance & Outcomes

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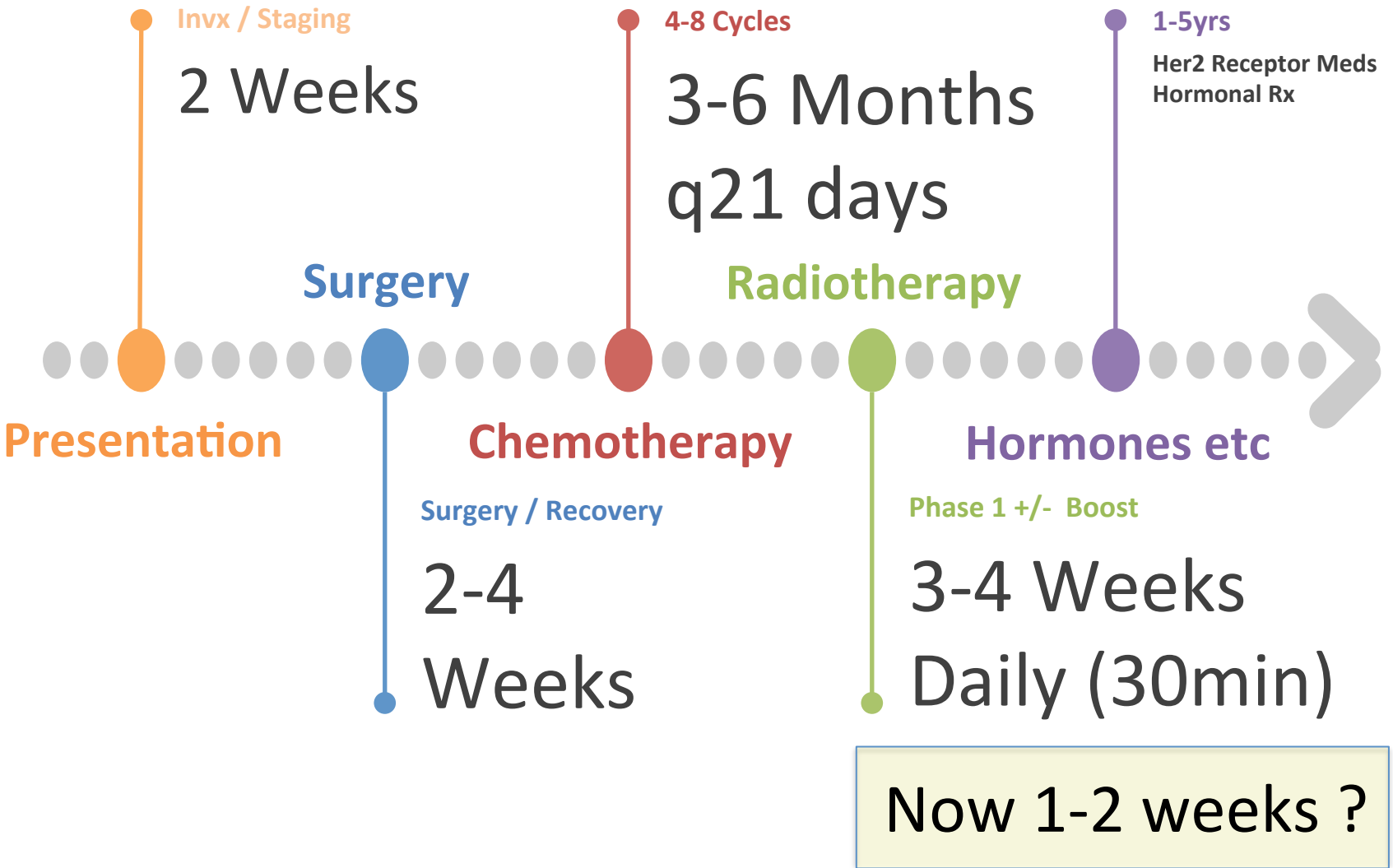
6-9 Month Treatment Course From Diagnosis to End of RT



Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

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From Bench to Bedside…

- Within the fraternity, this was an elegant demonstration of ‘bench to bedside’ radiobiological research leading to radical change in the practice of Radiotherapy
- Cell Survival Curves > Radiobiological Modeling > Hypothesis Generation > Clinical Trials > Biostatistics
- At the Heart, this was Brains and Biology (Classical British Style), delivered by Modern Technology

Concept and Results of the Lancet Paper

- Aim: To identify a 5 fraction schedule of adjuvant radiotherapy delivered in 1 week that is non-inferior in terms of local control and is as safe as an international standard 15 fraction regimen after primary surgery for early breast cancer

- Multicentre, phase 3, randomised, non-inferiority trial done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK.

- Patients aged at least 18 years with invasive carcinoma of the breast (pT1-3, pN0-1, M0) after breast conservation surgery or mastectomy.

Concept and Results of the Lancet Paper

Whole breast or chestwall treatment, randomly allocated to:

- 40Gy in 15 fractions over 3 weeks (2.67 Gy per fraction)
- 27Gy in 5 fractions over 1 week (5.4Gy per fraction)
- 26Gy in 5 fractions over 1 week (5.2Gy per fraction)

Concept and Results of the Lancet Paper

Primary endpoint:

- Ipsilateral breast tumor relapse
- Assuming a 2% 5 year incidence for 40Gy, non-inferiority was predefined as ≤ 1.6% excess for five fraction schedules (critical Hazard ratio [HR] of 1.81

Normal tissue effects were assessed by clinicians, patients and from photographs

Concept and Results of the Lancet Paper

	Cumulative number of events	Estimated cumulative incidence by 5 years (95% CI)	Hazard ratio (95% CI); p value	Estimated absolute difference vs 40 Gy at 5 years (95% CI)
Ipsilateral breast tumour (local) relapse*				
40 Gy (n=1361)	31 (2·3%)	2·1% (1·4 to 3·1)	1 (ref)	..
27 Gy (n=1367)	27 (2·0%)	1·7% (1·2 to 2·6)	0·86 (0·51 to 1·44); 0·56	−0·3% (−1·0 to 0·9)
26 Gy (n=1368)	21 (1·5%)	1·4% (0·9 to 2·2)	0·67 (0·38 to 1·16); 0·15	−0·7% (−1·3 to 0·3)

N= 4110
ITT Analysis= 4096
Median f/u 71.5 mths

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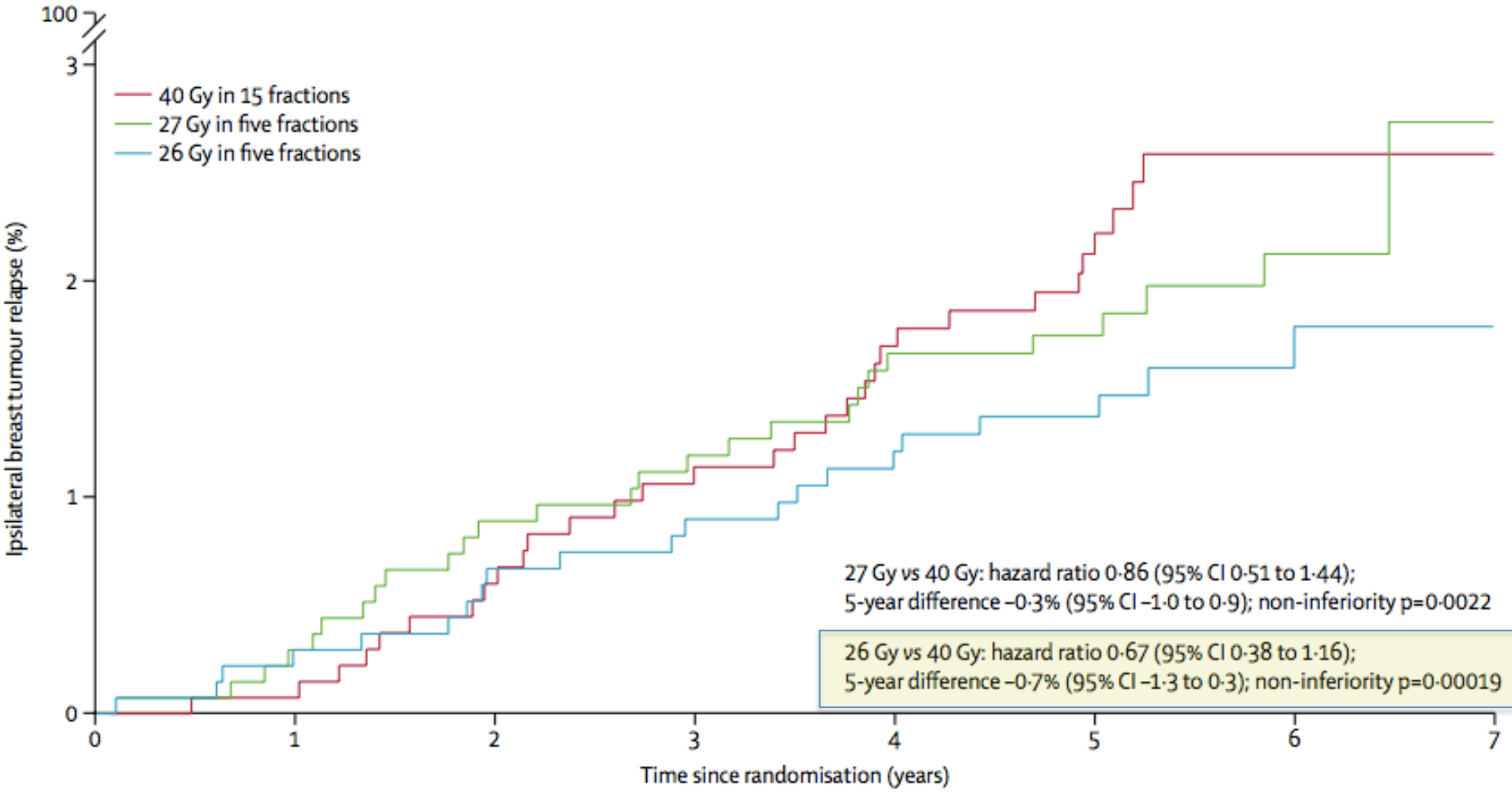
Concept and Results of the Lancet Paper



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Concept and Results of the Lancet Paper

- '5-year ipsilateral breast tumour relapse incidence after a 1-week course of adjuvant breast radiotherapy delivered in five fractions is non-inferior to the standard 3-week schedule according to the predefined inferiority threshold.'

- 'The 26 Gy dose level is similar to 40 Gy in 15 fractions in terms of patient-assessed normal tissue effects, clinician-assessed normal tissue effects, and photographic change in breast appearance'

- This is generally true @5yrs, and by way of their analysis

	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)

- Clinician Assessment looked at: Breast distortion, shrinkage, induration, telangiectasia, odema, discomfort
- Small Number of events, thus moderate/marked put together for analysis
- Generally <5%

Concept and Results of the Lancet Paper

Any moderate or marked clinician assessed normal tissue effects in the breast or chest wall :

- 98 out of 986 patients (9.9%) in 40Gy
- 121 out of 1020 patients (11.9%) in 26Gy

Across all clinician assessments from 1-5 years, odds ratios versus 40Gy in 15 fractions was 1.12 (0.94 to 1.34, p=0.2) for 26Gy

Concept and Results of the Lancet Paper

- Patient and photographic assessments did not show higher normal tissue effect risk for for 26Gy versus 40Gy.
- Very low rate of cardiac events, rib fracture and symptomatic lung fibrosis.

Table A5: Change in photographic breast appearance at 2 and 5 years (breast conservation surgery patients) by fractionation schedule: results of longitudinal analysis for 1309 patients with photographic assessments at 2 and/or 5 years

	2 years				5 years				OR for mild / marked change vs 40Gy (95%CI)	Comparison with 40 Gy; p-value[1]	Comparison between 27 Gy & 26 Gy; p-value[1]
	N	None (%)	Mild (%)	Marked (%)	N	None (%)	Mild (%)	Marked (%)			
40 Gy / 15Fr	411	376 (91.5)	33 (8.0)	2 (0.5)	283	249 (88.0)	33 (11.7)	1 (0.3)	1	-	-
27 Gy / 5Fr	429	362 (84.4)	48 (11.2)	19 (4.4)	308	225 (73.1)	70 (22.7)	13 (4.2)	2.29 (1.60, 3.27)	<0.0001	-
26 Gy / 5Fr	427	381 (89.2)	33 (7.7)	13 (3.0)	284	247 (87.0)	28 (9.9)	9 (3.2)	1.26 (0.85, 1.86)	0.24	0.0006

[1] p-value from Wald test; OR = odds ratio (estimated from GEE model including 2 and 5-year data); 95%CI=95% confidence interval

Table A7: Incidence of other late adverse effects, by fractionation schedule

	40 Gy N=1361 (%)	27 Gy N=1367 (%)	26 Gy N=1368 (%)
Symptomatic rib fracture			
Reported[1]	14 (1.0)	25 (1.8)	20 (1.5)
Confirmed[2]			
Total	6 (0.4)	13 (1.0)	12 (0.9)
Ipsilateral side	*5 (0.4)*	*11 (0.8)*	*8 (0.6)*
Symptomatic lung fibrosis			
Reported[3]	9 (0.7)	10 (0.7)	10 (0.7)
Confirmed[2]			
Total	6 (0.4)	9 (0.7)	7 (0.5)
Ipsilateral side	*4 (0.3)*	*8 (0.6)*	*5 (0.4)*
Ischaemic heart disease			
Reported[4]	13 (1.0)	17 (1.2)	24 (1.7)
Confirmed[2]			
Total	12 (0.9)	11 (0.8)	10 (0.7)
Left-sided	*6 (0.4)*	*8 (0.6)*	*3 (0.2)*

[1] Reported cases of symptomatic rib fracture include 8 not radiotherapy-related (5 trauma, 1 metastases, 1 osteopenia, 1 reason not given but stated to be not due to radiotherapy)

[2] After imaging and further investigations; excluding cases not radiotherapy-related

[3] Reported cases of symptomatic lung fibrosis include 2 not radiotherapy-related (1 secondary to infection and 1 GI COPD)

[4] Reported cases of ischaemic heart disease include 17 patients with pre-existing heart disease at randomisation

Concept and Results of the Lancet Paper

- 'The consistency of FAST-Forward results with earlier hypofractionation trials supports the adoption of 26 Gy in five daily fractions as a new standard for women with operable breast cancer requiring adjuvant radiotherapy to partial or whole breast.' (Note RNI sub-study results are not out yet)

- With the caveat that safety is in terms of normal tissue effects documented at up to 5 years

- You will note that Side Effects are actually quite low and not life-threatening

	Number of moderate or marked events/total number of assessments over follow-up
Any adverse event in the breast or chest wall*	..
40 Gy	651/6121 (10·6%)
27 Gy	1004/6303 (15·9%)
26 Gy	774/6327 (12·2%)

What is more?

- **Breast distortion**
- **Breast shrinkage**
- **Breast induration**
- **Telangiectasia**
- **Breast/chest wall oedema**
- **Breast chest wall discomfort**
- ***NOT STATISTICALLY SIGNIFICANT**

What is less?

- **Acute RTOG Grade 3 toxicity**
- **6/44 (13.6%) in 40Gy**
- **3/52 (5.8%) in 26Gy**

Effect of Time ?

Clinical Adoption and Application

- UK – Standard Practice, Boost in 2-4 #
- US – Option
- Sg – Public, Yes, even nodal?

- Considerations:

- Institution A: Low Risk Patients (Post-menopausal with ER+ve) not requiring boost, otherwise use 3-4 week regime

- Institution B: Implemented due to situation

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic

Giuseppe Curigliano [a, b, 1, *], Maria Joao Cardoso [c, d], Philip Poortmans [e, f], Oreste Gentilini [g], Gabriella Pravettoni [a, b], Ketti Mazzocco [a, b], Nehmat Houssami [h], Olivia Pagani [i], Elzbieta Senkus [j], Fatima Cardoso [c], on behalf of the editorial board of The Breast

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3. Deliver RT in 5 fractions for all patients requiring RT with node negative tumours that do not require a boost. Options include 28–30Gy in one weekly fraction over 5 weeks or 26Gy in 5 daily fractions over 1 week as per the FAST and FAST Forward trials, respectively [22–24].

Advances in Radiation Oncology (2020) xx, 1-7

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Critical Review

Breast Radiation Therapy Under COVID-19 Pandemic Resource Constraints—Approaches to Defer or Shorten Treatment From a Comprehensive Cancer Center in the United States

Lior Z. Braunstein, MD,[a,*,1] Erin F. Gillespie, MD,[a,b,1] Linda Hong, MD,[c] Amy Xu, MD,[a] Samuel F. Bakhoum, MD,[a,d] John Cuaron, MD,[a] Boris Mueller, MD,[a] Beryl McCormick, MD,[a] Oren Cahlon, MD,[a] Simon Powell, MD,[a] and Atif J. Khan, MD[a]

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Received 24 March 2020; revised 25 March 2020; accepted 25 March 2020

Table 1 Hypofractionated or accelerated breast radiation therapy regimens

Target	Total dose/no. of fractions	Technique/contours	Dose constraints (for shortest regimen only)	Notes
Partial breast	30 Gy/5 every other day (preferred) or daily (acceptable) 40 Gy/10 daily	IMRT/VMAT (preferred) 3D-CRT GTV (clips*) to PTV ~2 cm (1.5 cm to CTV with 5 mm PTV margin)	30 Gy in 5 fractions: D_{max} <110% V105%(31.5 Gy) <5% of breast volume Ipsi breast-PTV V15Gy <50% Contra breast D_{max} <1Gy Lung (ipsi) V10Gy <20% Lung (contra) V5Gy <10%	Florence PBI trial[22] http://econtour.org/cases/47 MSK prospective[25,26] http://econtour.org/cases/108 * Clips strongly preferred for targeting and daily setup * Daily kv match to clips vs CBCT match to seroma
Whole breast	26 Gy/5 daily ± 5.2 Gy × 1 boost 40 Gy/15 daily 42.4 Gy/16 daily	3D-CRT For left-sided, DIBH (preferred) and/or heart block	26 Gy in 5 fractions: D_{max} <110% V107% <2% of breast volume V105% <5% of breast volume Lung V8Gy <15% (<17% acceptable) Heart V7Gy <5%, V1.5Gy <30%	UK FAST FORWARD[35] http://econtour.org/cases/117
Postmastectomy (PMRT)	42.56 Gy/16	3D-CRT or IMRT	42.56 Gy in 16 fractions: D_{max} <115% V107% <10 cm^3 of PTV Contra breast V3Gy <10% (preferred), V5Gy <10% (acceptable) Lung V18Gy ≤35% (≤40% acceptable) Heart mean ≤3 Gy (preferred), ≤5 Gy (acceptable) Heart V22.5Gy <10% (left-sided), V22.5Gy <2% (right-sided)	RTCHARM (NCT03414970) http://econtour.org/cases/110
Breast and RNI	42.56 Gy/16 with SIB to tumor bed 48 Gy/16 (3 Gy/fx) 40 Gy/15 with SIB† to tumor bed 48 Gy/15 (3.2 Gy/fx)	3D-CRT or IMRT 3D CRT SIB involves a separate electron plan delivered after photon plan Seroma/clips 7-10 mm for CTV, then another 5-7 mm for PTV. NOTE: expansions can be smaller for SIB.	(see PMRT constraints)	UK START B[33] and extrapolation from RTOG 1005[50] †SIB: EQD2 57Gy for a/b 3

Abbreviations: 3D-CRT = 3D conformal radiation therapy; CBCT = cone beam computed tomography; CTV = clinical target volume; DIBH = deep inspiration breath hold; GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; MSK = Memorial Sloan Kettering; PBI = partial breast irradiation; PMRT = post-mastectomy radiation; PTV = planning target volume; RNI = regional nodal irradiation; RTOG = Radiation Therapy Oncology Group; SIB = simultaneous integrated boost; VMAT = volumetric modulated arc therapy.

For illustrative case presentations and guidance in contouring and planning the various regimens described, including target volumes, organs at risk, and relevant expansions, please visit http://econtour.org/hypofrac. Online cases also include dosimetric guidance and the dose constraints used in various supportive protocols.

Clinical Adoption and Application

Reasons for Caution:

- > 80% in FF > 50yrs
- Late side effects are not better compared to 40Gy
- In PROM and Photographic substudy only 1796 and 1736 patients (accrual needed was 2196)
- 10 year follow up to see the trend of late effects
- Data from Lymph nodal radiotherapy sub-study started in 2015 awaited
- Widespread adoption of 40Gy/15Fractions happened after multiple RCTs, >7000 patients data and 10 year follow ups.

Breast Cancer Overview

Age Distribution of Breast Cancer Patients, 2006 – 2015

Age group	2006-2010		2011-2015	
	No. of cases	%	No. of cases	%
0-44	1,928	24.6	1,838	19.1
45-54	2,649	33.8	2,778	28.8
55-64	1,765	22.5	2,747	28.5
65-74	922	11.8	1,419	14.7
75+	571	7.3	852	8.8
Total	7,835	100.0	9,634	100.0

vs 20% under 50 in UK in 2010

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Breast Cancer Overview

Stage Distribution of Breast Cancer Patients, 2006 – 2015

Stage	2006-2010		2011-2015	
	No. of cases	%	No. of cases	%
I	2,440	33.2	2,868	32.7
II	2,804	38.2	3,375	38.5
III	1,403	19.1	1,620	18.5
IV	697	9.5	910	10.4

* Cancers of unknown stage were excluded.

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Breast Cancer Overview

Stage	2006-2010		2011-2015	
	ASOS (95% CI)	ASRS (95% CI)	ASOS (95% CI)	ASRS (95% CI)
I	90.98 (89.52, 92.24)	100.73 (99.11, 102.12)	90.59 (89.44, 91.63)	100.08 (98.81, 101.22)
II	81.07 (79.34, 82.66)	90.21 (88.30, 91.99)	80.05 (78.62, 81.40)	89.12 (87.52, 90.62)
III	58.94 (56.01, 61.74)	66.24 (62.95, 69.39)	64.88 (62.42, 67.22)	72.25 (69.51, 74.86)
IV	20.20 (16.70, 23.94)	22.53 (18.63, 26.71)	20.97 (18.19, 23.90)	23.04 (19.98, 26.25)
All	**68.66 (67.63, 69.67)**	**78.09 (76.91, 79.24)**	**70.84 (69.93, 71.72)**	**79.73 (78.71, 80.72)**

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Clinical Adoption and Application

- My Algorithm:

- Use for Breast / Chest Wall Only (no RNI)
- Main concern is Toxicity to Breast (Whole point of BCS)
- Age > 50yrs
- No Risk Factors for More severe toxicity (ie TGFB1 variant, infection etc)
- OK with Boost (prob not integrated)
- Strict Planning Standards and Daily Onsite IGRT

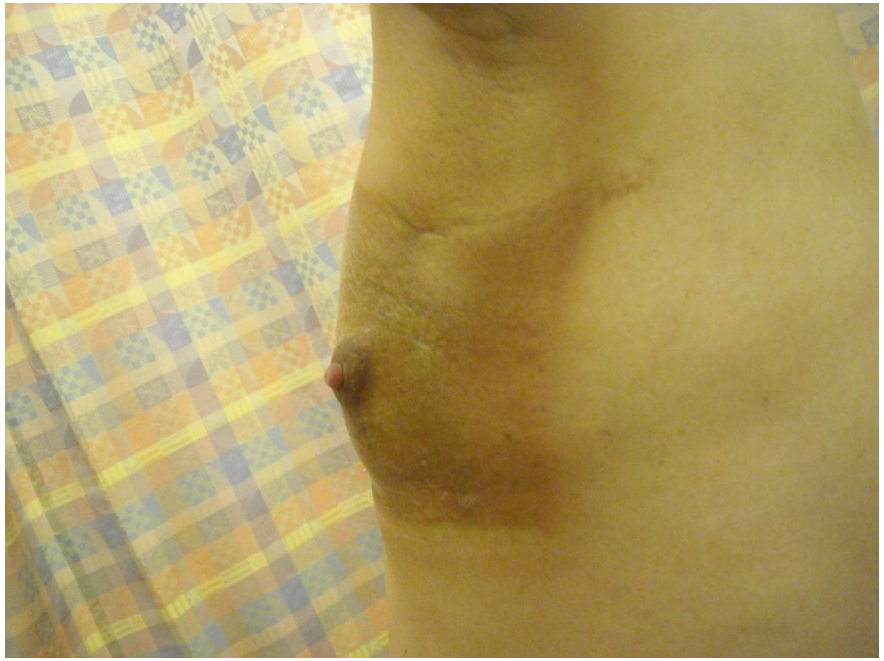
Clinical Adoption and Application

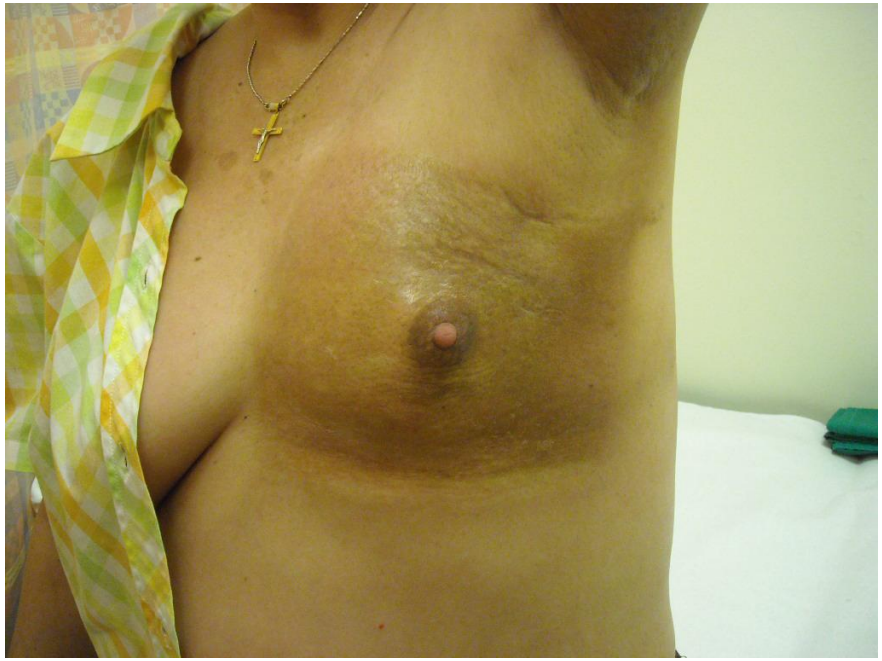
- What you can't see can hurt you
- Acute Reactions are better!
- Look at fine print on fall out
- Prescription point matters, ie diff between 26 vs 27 is only 3.8%

What is less?

- **Acute RTOG Grade 3 toxicity**
- **6/44 (13.6%) in 40Gy**
- **3/52 (5.8%) in 26Gy**

Clinical Adoption and Application





- Standard 50Gy/25# + 10Gy Boost 8/2/10-25/3/10
- Pain at Lt UOQ 6mths later. Pain, redness and warmth not responding to antibiotics
- Extensive invx for disease as well as CTD − NED, Symptomatic Rx given
- By June 2011, Inflammation had resolved, but pain due to tightness persisted

Genomics for life

Focusing on
Personalised Medicine

RADIATION SENSITIVITY ASSAY

The Radiation Sensitivity Assay may help determine if you have the *TGFβ1* genetic variation associated with a low or high risk of developing fibrosis. This information may be helpful when deciding whether to give a tumour bed boost after whole-breast radiation, as a boost increases the risk of fibrosis while modestly decreasing recurrence risk. [1]

What is Radiation-Induced Fibrosis?

Radiation-induced fibrosis (RIF) is a long-term side effect of external beam radiation therapy for the treatment of cancer. [2] RIF usually appears 4 – 12 months after radiation therapy and may progress over several years. [2] The clinical presentation depends on the type of tissue exposed to irradiation. The development of RIF can be described as a "wound-healing response gone wrong", and may manifest as skin induration and thickening, muscle shortening and atrophy, limited joint mobility, lymphedema, mucosal fibrosis, ulceration, fistula, hollow organ stenosis and pain – all of which can significantly impact a patient's quality of life. [2,3]

Research

JAMA Oncology | Original Investigation

Association of Transforming Growth Factor β Polymorphism C–509T With Radiation-Induced Fibrosis Among Patients With Early-Stage Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

Aaron J. Grossberg, MD, PhD; Xiudong Lei, PhD; Ting Xu, PhD; Simona F. Shaitelman, MD, MEd; Karen E. Hoffman, MD, MHSc, MPH; Elizabeth S. Bloom, MD; Michael C. Stauder, MD; Welela Tereffe, MD, MPH; Pamela J. Schlembach, MD; Wendy A. Woodward, MD, PhD; Thomas A. Buchholz, MD; Benjamin D. Smith, MD

Supplemental content

IMPORTANCE Whether genetic factors can identify patients at risk for radiation-induced fibrosis remains unconfirmed.

OBJECTIVE To assess the association between the C–509T variant allele in the promoter region of *TGFB1* and breast fibrosis 3 years after radiotherapy.

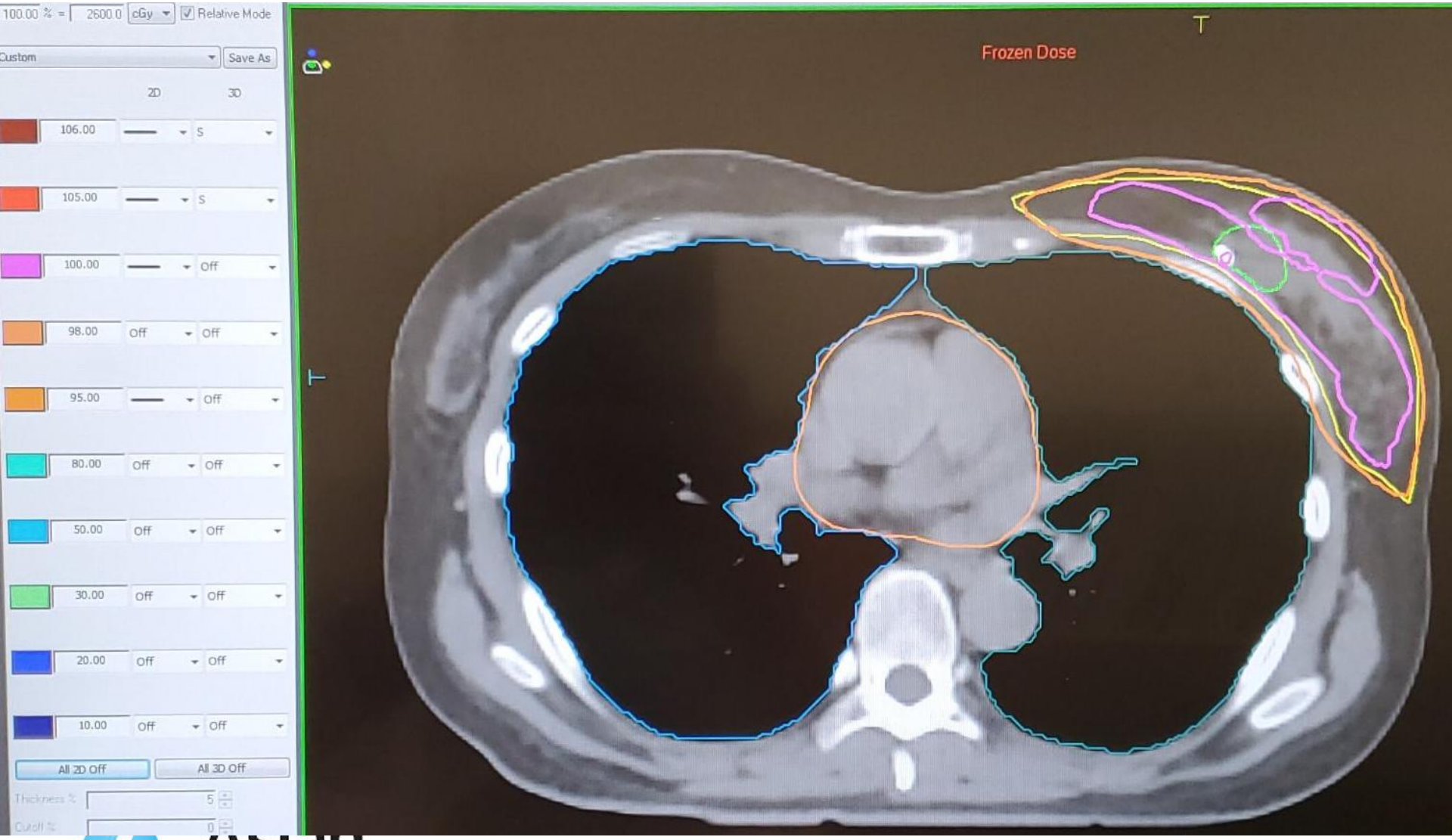
What causes Radiation-Induced Fibrosis?

There have been several studies that suggest the radiosensitivi
factors. [1,4-6] The C–509T *TGFβ1* variant allele may be used as a
elevated risk for fibrosis following radiotherapy. [1]

Transforming growth factor-b1 (*TGFβ1*) is the major cytokine re
proliferation and differentiation. [6] Differentiated fibroblasts syn
the extracellular matrix, and it has been suggested that an increase in these fibroblasts may trigger the development of fibrosis. [6]

Radiation induces long-term *TGFβ1* overexpression due to oxidative stress and an inflammatory response. [6] Elevated serum *TGFβ1* levels were correlated with an increased risk of fibrosis in breast and lung cancer patients, and a comparison of the genotypes of unaffected and affected patients has been genetically associated with variants in the *TGFβ1* gene. [6]

Concept and Results of the Lancet Paper



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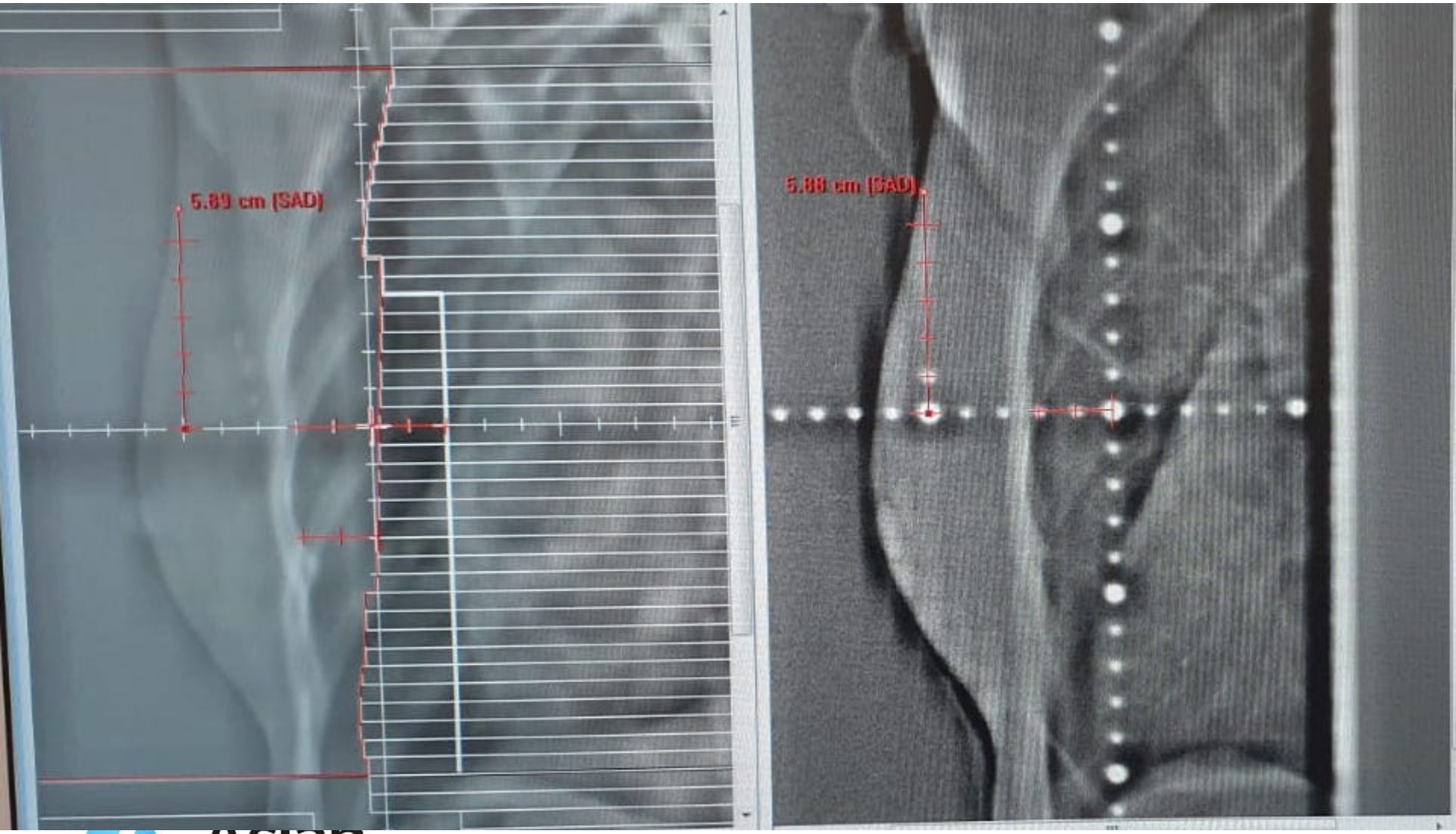
Concept and Results of the Lancet Paper



Concept and Results of the Lancet Paper

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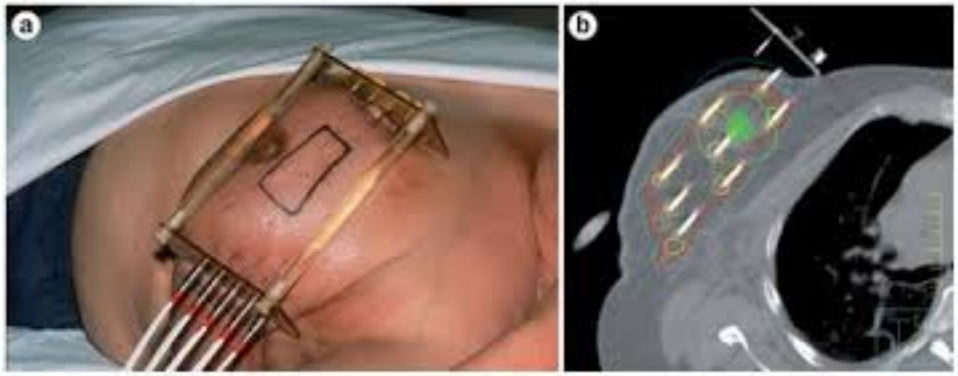
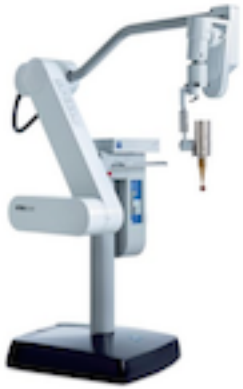
Evolution of Local Therapy of Breast Cancer

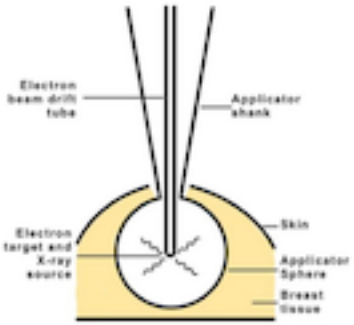
- Quest for: Improved Survival, Reduced Toxicity
- Since early 2000s many attempts were made to Minimize Downtime

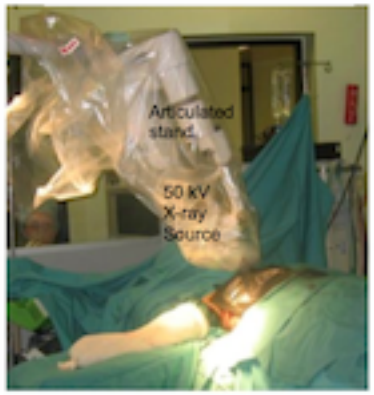
- APBI- Accelerated Partial Breast RT
- Strict Selection Criteria
- Complex Logistics, Cost etc

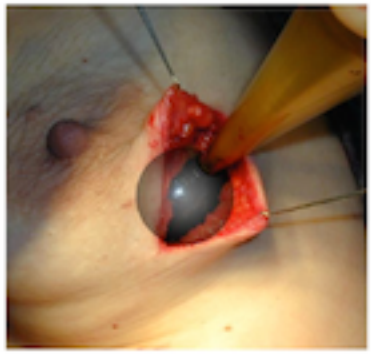


Brachytherapy (8-10 sessions over 4-5 days)









IORT – Intra-operative RT (~30min Intra-op)

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Future Directions and Conclusion

- ‘False Starts’ have finally found their solution
- External Beam APBI most suitable technique, moving forward
- Potential to do RT upfront then continue Chemo after…
- Await data on Regional Nodal Irradiation
- Paves the way for similar schedule reduction in Other Cancers and Anatomical Sites

Future Directions and Conclusion

- Less is more, is indeed an apt saying for Mx of Ca Breast
- 5 day Whole Breast or Chest Wall RT is now a ready option for local therapy of Early Ca Breast
- Efficacy is clearly non-inferior to international standard of 15#
- Toxicity is most probably not increased, but we await confirmation of 10yr data
- A significant number of patients will be fully eligible for this regime and should be offered as such
- Those who are keen but who may be at increased risk of toxicity should not risk it and continue on the 15# RT until more data is analysed

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https://www.aamg.co/aaro/
81013838

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Download Slides at www.oncologyschool.com/breast

Thank You!

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