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Close to the Heart

Modern Radiation Therapy for Breast Cancer Treatment

Joanna C. Yang MD MPH
Nicolas Prionas MD PhD
Florence Yuen RN MSN AOCNP

10/22/2020

Learning Objectives

- Describe the ways in which new technology can help us to better protect the heart during radiation therapy for breast cancer

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- Become familiar UCSF's unique approach towards skin care in breast cancer patients

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Cardiac Sparing Techniques for Breast Cancer Patients

Joanna Yang MD MPH

Learning Objectives

- **Describe the ways in which new technology can help us to better protect the heart during radiation therapy for breast cancer**
- Understand the stepwise progress towards shorter courses of treatment for breast cancer patients
- Become familiar UCSF's unique approach towards skin care in breast cancer patients

Background

- Data from the 1980s suggest that adjuvant radiation therapy in breast cancer patients may have adverse effects in long-term survivors

Patient enrolment, years	Increase in risk for cardiac death (hazard ratio) in follow-up			
	Up to 10 years	10–14 years	15–19 years	≥ 20 years
1973–1982	*1.19*	*1.35*	*1.64*	*1.90*
1983–1992	0.99	1.02	1.11	1.21
1993–2002	0.97	0.99		no data
2003–2008	1.00	no data	no data	no data

Cuzick J, et al. Cancer Treat Rep 1987

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Background

- The Early Breast Cancer Trialists' Collaborative Group first published on the dose effect for cardiac toxicity in 2005

Heart dose, range (mean)	Total number of patients	Cardiac events in irradiated patients	Cardiac events in non-irradiated patients	Hazard ratio for annual risk
0–5 Gy (3 Gy)	9,982	2.9%	2.4%	1.08 (n.s.)
5–15 Gy (9 Gy)	7,850	5.4%	3.8%	1.32
> 15 Gy (17 Gy)	2,265	11.0%	6.4%	1.63

Clarke M, et al; EBCTCG. Lancet 2005.

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Background

- Population-based case-control study of coronary events in **2168 women** in Sweden and Denmark who received RT for breast cancer between **1958-2001**
- Mean heart dose was **4.9Gy** (range 0.03 Gy to 27.72Gy)
- Mean heart dose to the whole heart was **estimated**

Darby SC, et al. N Engl J Med 2013.

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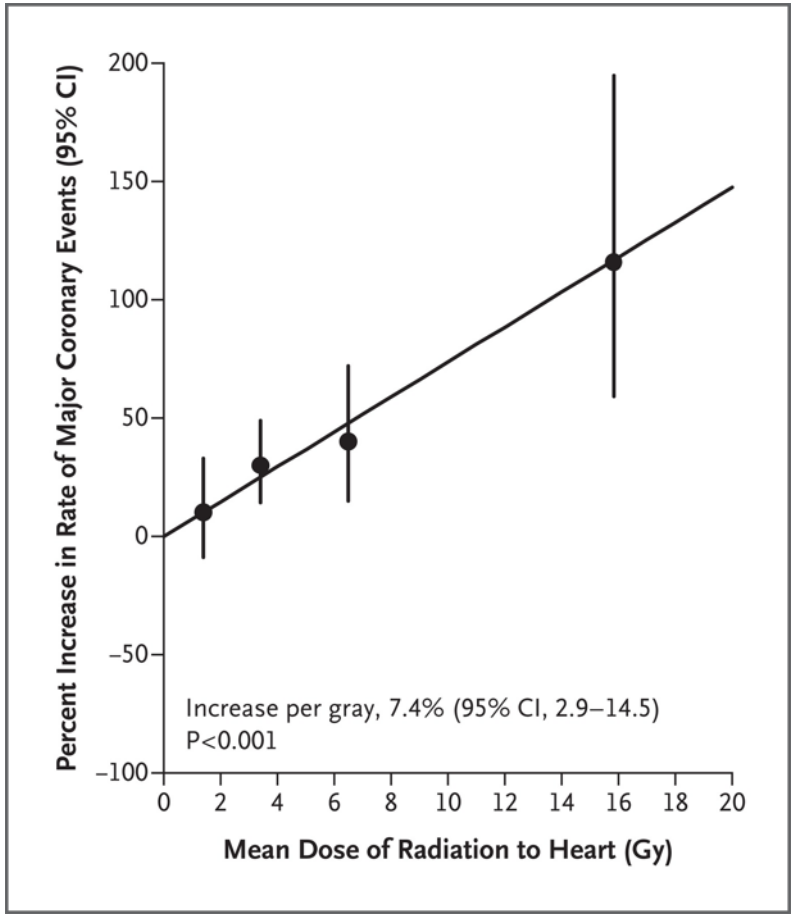
Background

- Rates of coronary events increased linearly with the mean heart dose by 7.4% per Gy



Darby SC, et al. N Engl J Med 2013.

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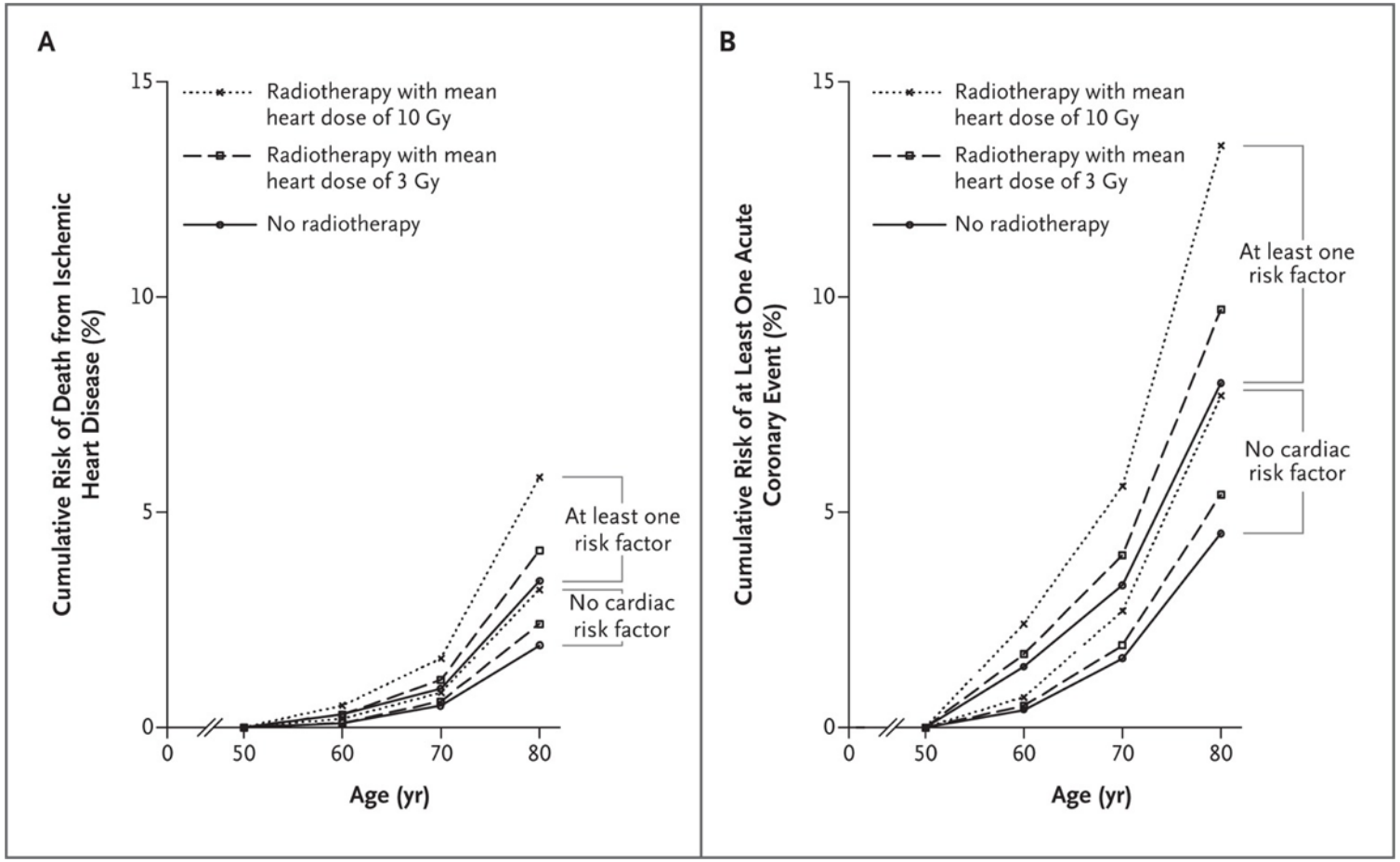

Darby SC, et al. N Engl J Med 2013.

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Background

- Supplementary materials provide tables with estimates of risk of cardiac death and coronary events by:
  - **Age**
  - **Mean Heart Dose**
  - **Presence of Cardiac Risk Factors**

Darby SC, et al. N Engl J Med 2013.

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Age at irradiation (years)	Mean heart dose (Gy)	No cardiac risk factor					At least one cardiac risk factor				
		Cumulative risk (%) by attained age				Absolute risk (%) of radiation-related IHD death by age 80 years	Cumulative risk (%) by attained age				Absolute risk (%) of radiation-related IHD death by age 80 years
		50	60	70	80		50	60	70	80	
40	0	0.03	0.1	0.5	2.0	0.0	0.08	0.3	0.9	3.3	0.0
	0.5	0.03	0.2	0.5	2.0	0.0	0.09	0.3	0.9	3.4	0.1
	1	0.03	0.2	0.6	2.1	0.1	0.09	0.3	1.0	3.5	0.2
	2	0.03	0.2	0.6	2.2	0.2	0.10	0.3	1.0	3.8	0.5
50	0		0.09	0.5	1.9	0.0		0.3	0.9	3.4	0.0
	0.5		0.09	0.5	2.0	0.1		0.3	1.0	3.5	0.1
	1		0.09	0.5	2.1	0.2		0.3	1.0	3.6	0.2
	2		0.10	0.5	2.2	0.3		0.3	1.1	3.8	0.4
60	0			0.2	1.6	0.0			0.7	3.0	0.0
	0.5			0.2	1.7	0.1			0.7	3.1	0.1
	1			0.2	1.7	0.1			0.8	3.2	0.2
	2			0.3	1.8	0.2			0.8	3.4	0.4
70	0				0.9	0.0				2.7	0.0
	0.5				0.9	0.0				2.8	0.1
	1				0.9	0.0				2.9	0.2
	2				1.0	0.1				3.1	0.4

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	2			0.3	1.8	0.2			0.8	3.4	0.4
70	0				0.9	0.0				2.7	0.0
	0.5				0.9	0.0				2.8	0.1
	1				0.9	0.0				2.9	0.2
	2				1.0	0.1				3.1	0.4

Evolution of Radiation Therapy

- Significant advancements in technology since the 1950s

1. Patients are immobilized
2. CT-based planning is performed (simulation)
3. Respiratory gating is used
4. In patients requiring lymph node treatment, intensity-modulated radiation therapy technique is a valuable tool

Treat What We Want to **Treat** & **Protect** What We Want to **Protect**

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Deep Inspiration Breath Hold

- DIBH describes a technique in which patients are asked to take a deep breath in and hold it during simulation and treatment

Main Benefits

1. Improved immobilization
2. More advantageous positioning of the breast and chest wall relative to the heart and lungs

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Outcome

Heart dose from LEFT sided breast RT looks like RIGHT sided breast RT

At Home Exercise

Figure: David Gilder

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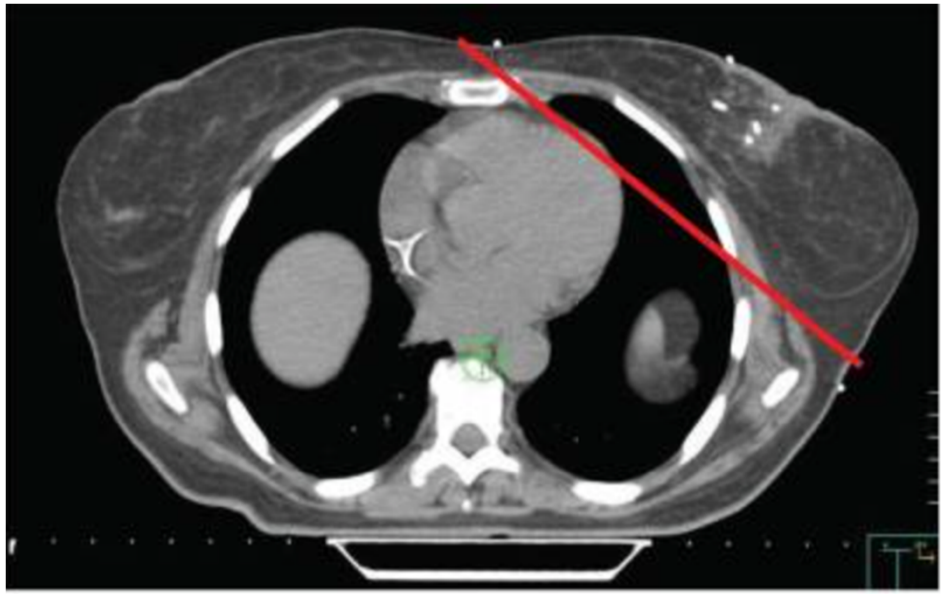
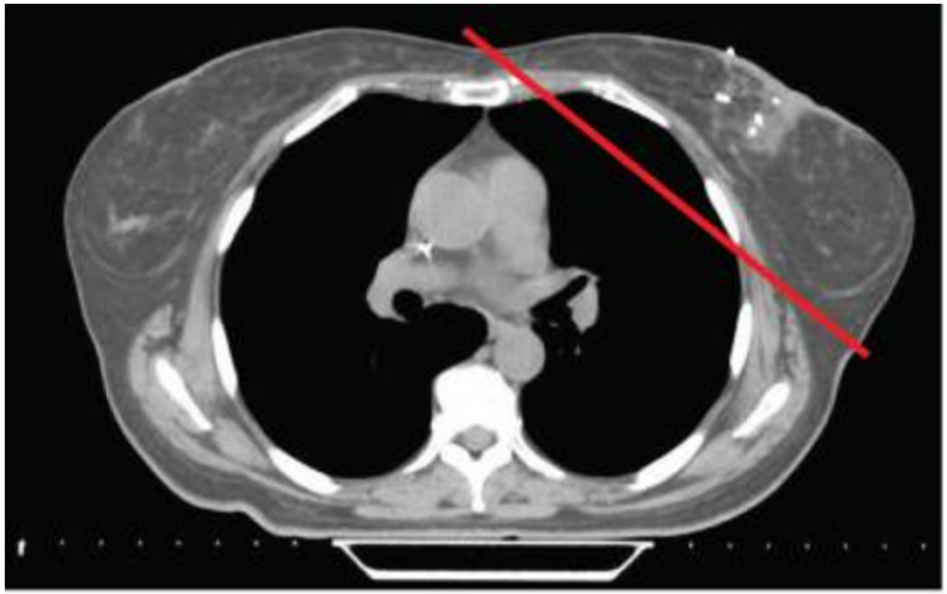
Deep Inspiration Breath Hold

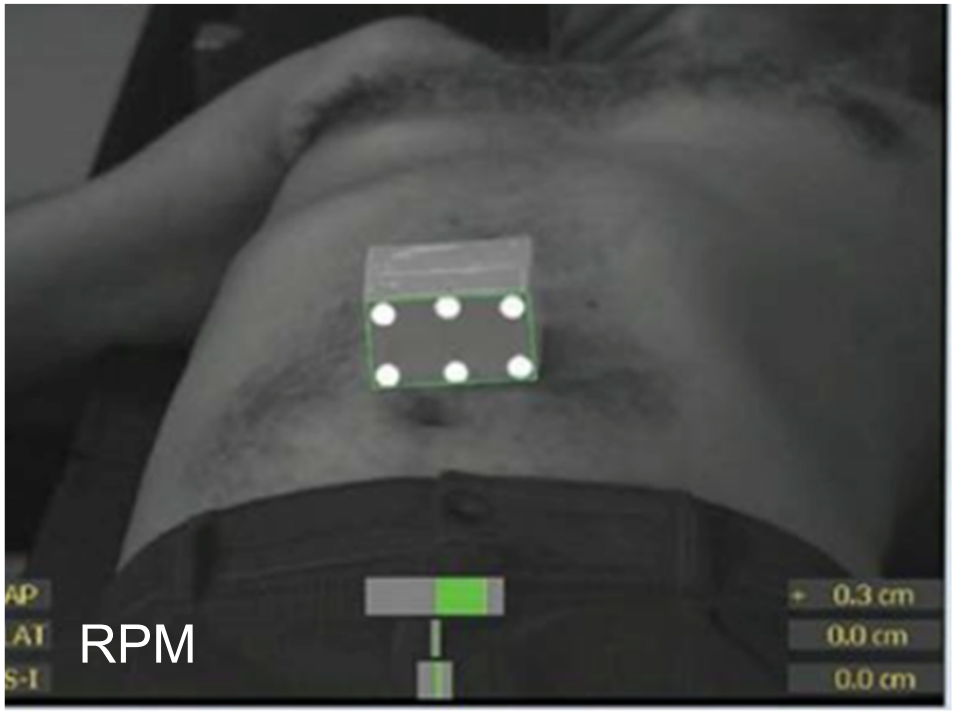


Free Breathing

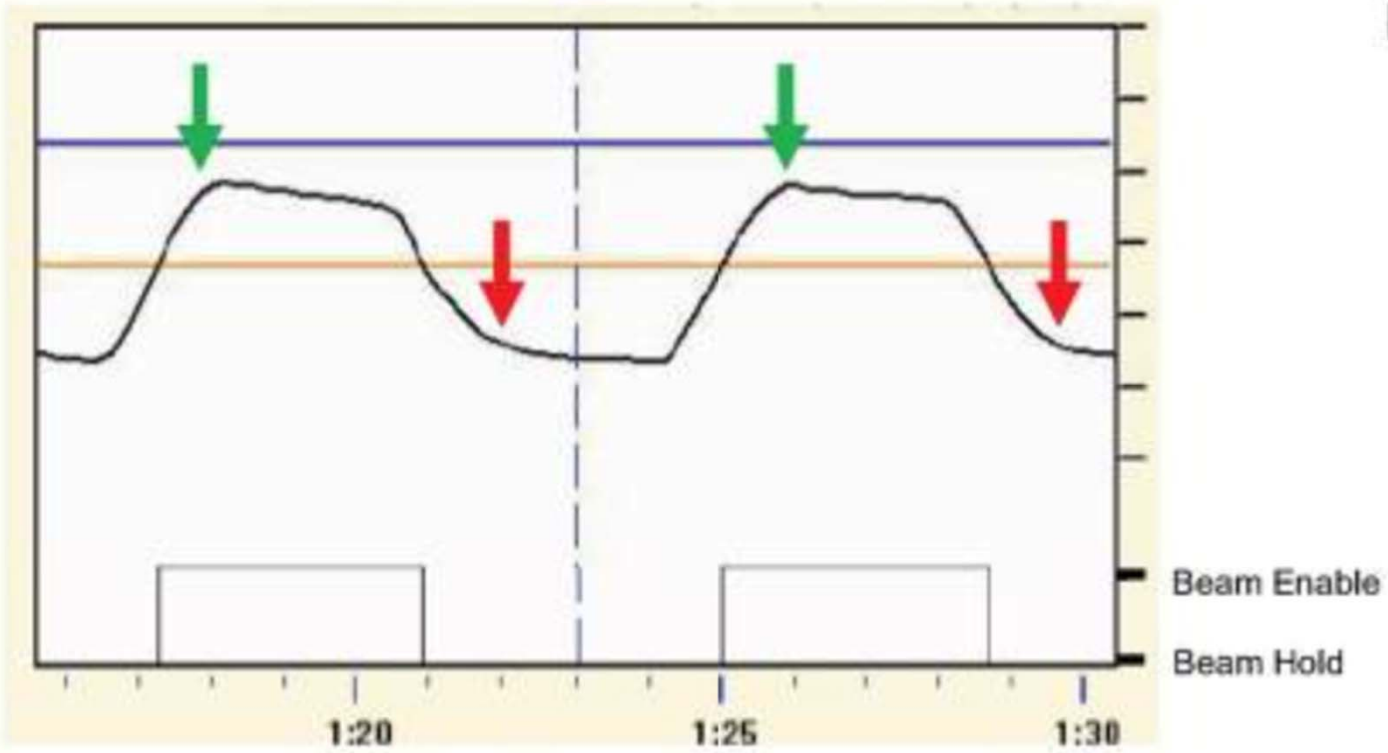


DIBH

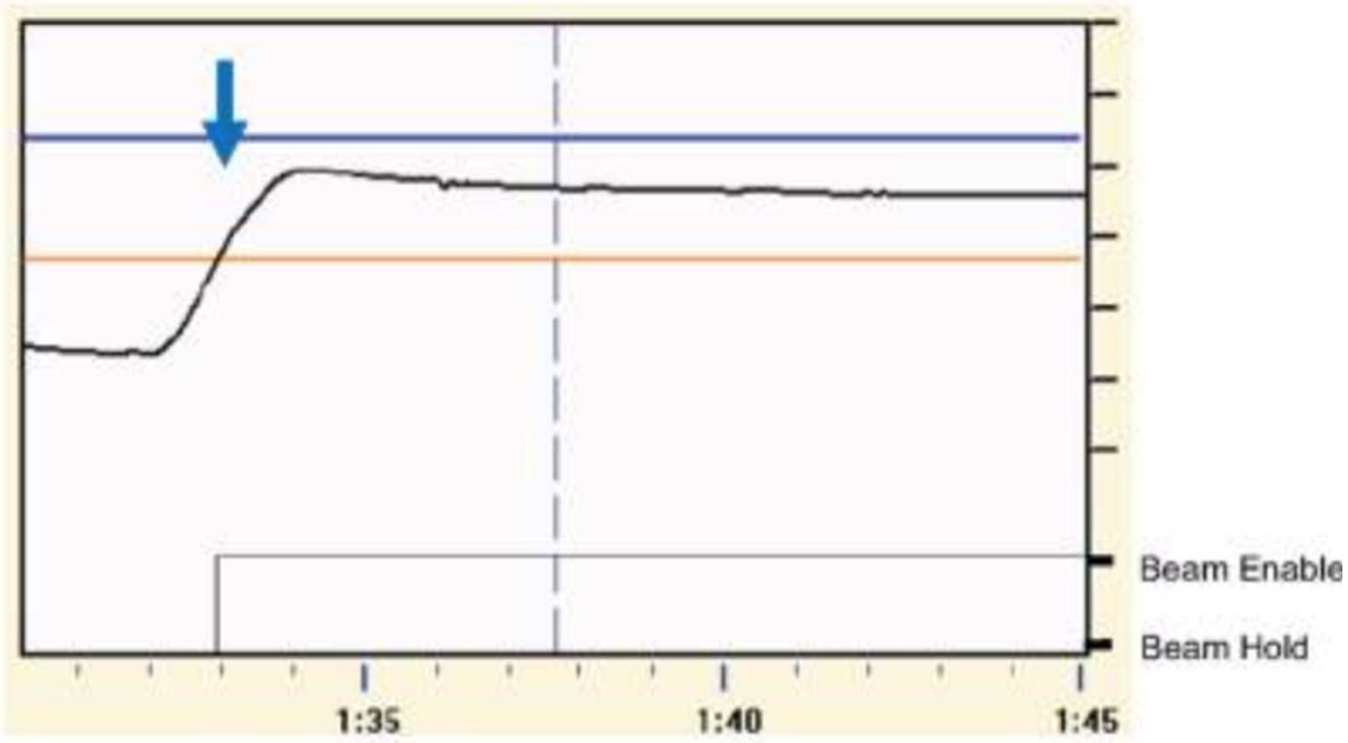
DIBH Systems

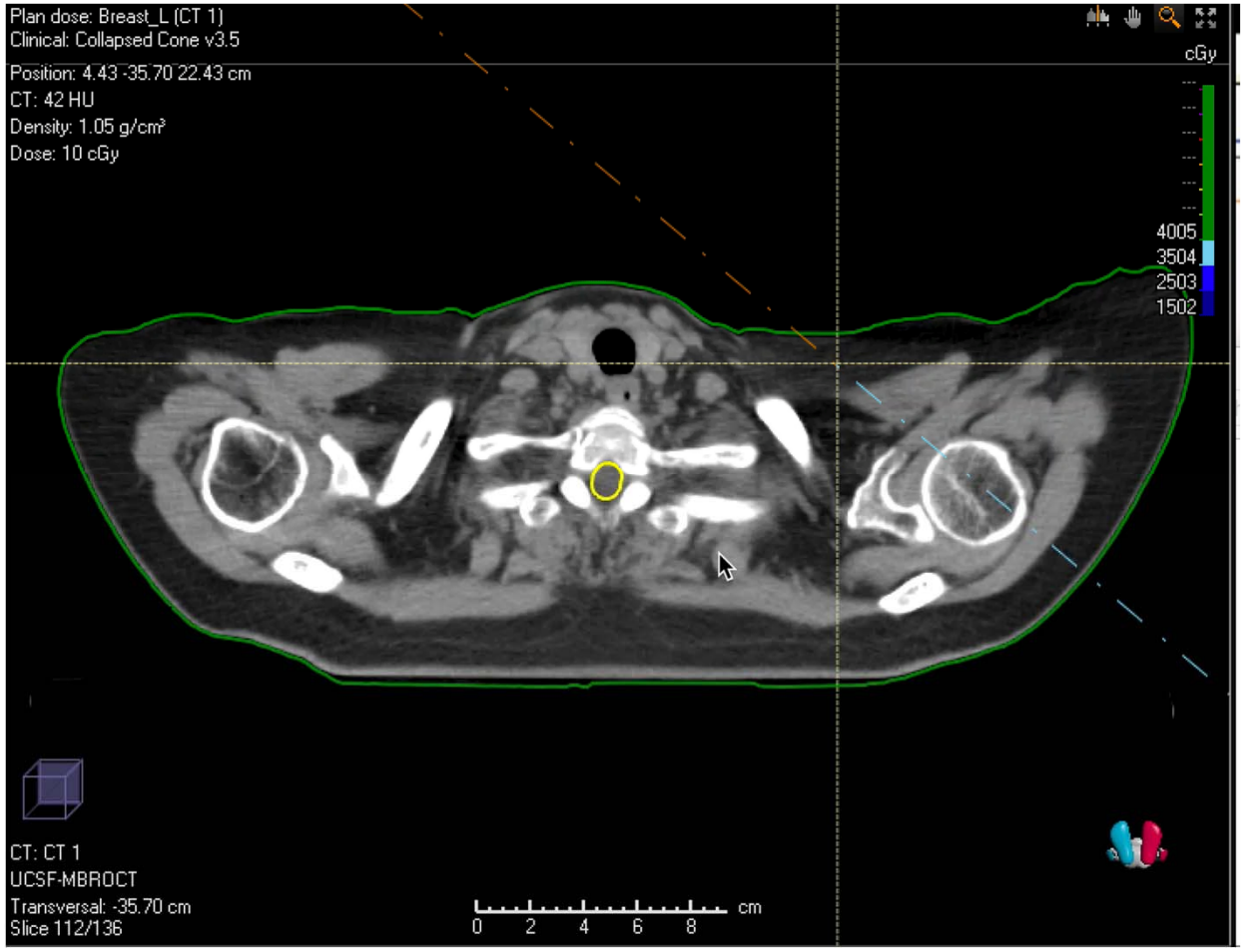


DIBH Process



DIBH Process





Mean Heart Dose
38cGy (0.38 Gy)

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Mean Heart Dose
29cGy (0.29 Gy)

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Evolution of Radiation Therapy

- Significant advancements in technology since the 1950s

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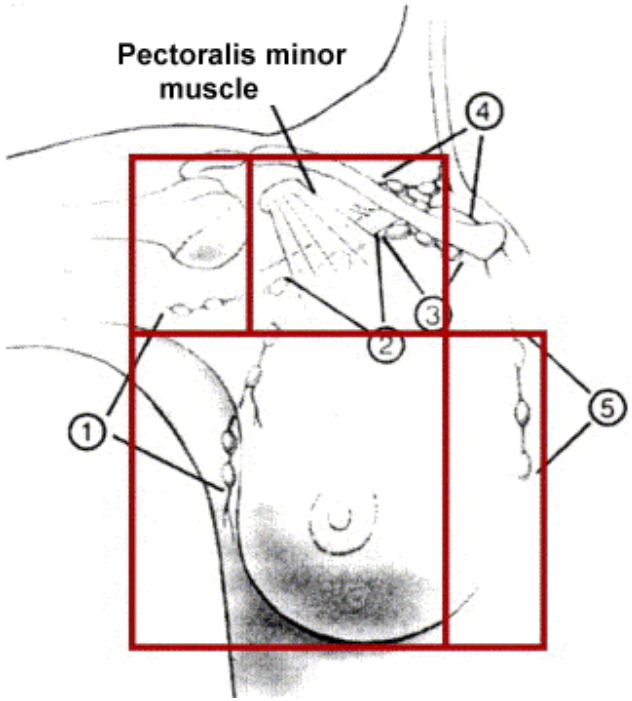
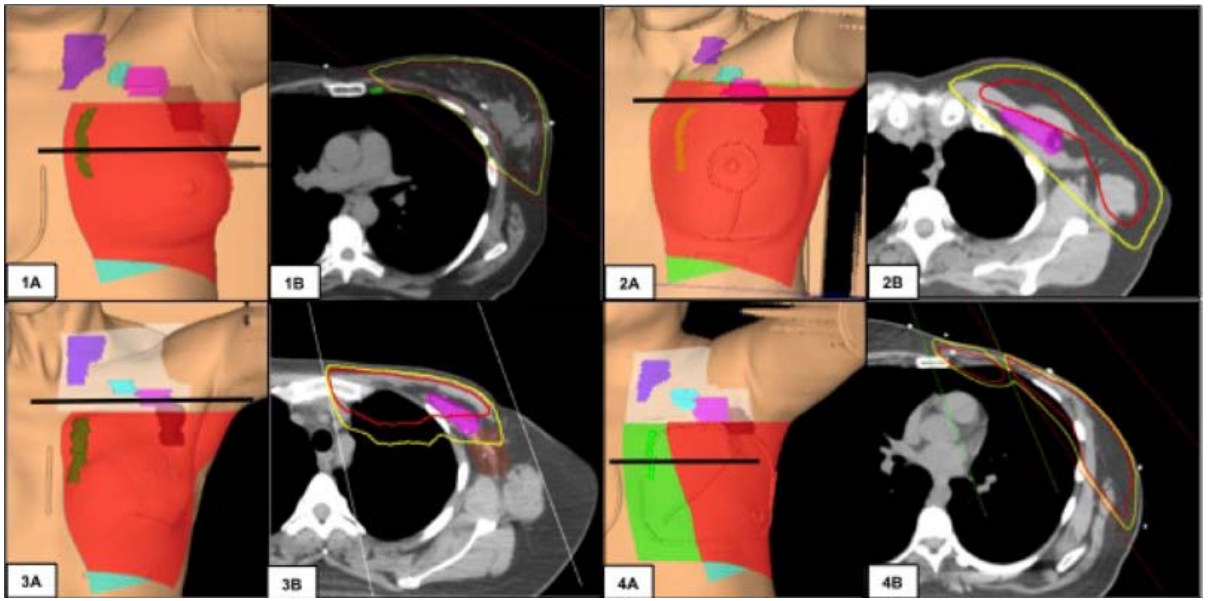
3. Respiratory gating is used
4. In patients requiring lymph node treatment, **intensity-modulated radiation therapy** technique is a valuable tool

Treat What We Want to **Treat** & **Protect** What We Want to **Protect**

Regional Nodal Irradiation





Yu PC, et al. Radiation Oncology 2018.

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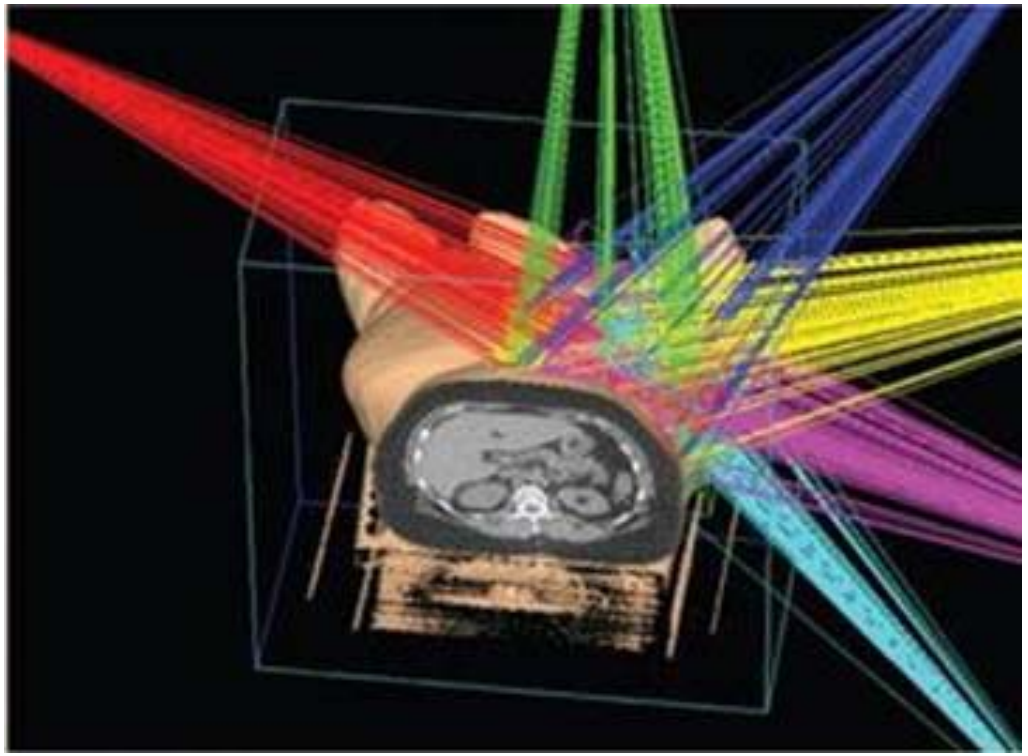
Intensity-Modulated Radiation Therapy

- IMRT is an **advanced form** of radiation therapy that delivers precise radiation doses to the target areas by **modulating the intensity** of the radiation beam in multiple small volumes
- Typically, IMRT requires **combinations of multiple intensity-modulated fields** coming from **different beam directions** to produce a customized radiation plan
- IMRT allows higher radiation doses to be focused on the tumor while minimizing the dose to surrounding normal critical structures

NB: Not necessary in early-stage, node-negative breast cancer

Intensity-Modulated Radiation Therapy



- We used 6-9 beams
- Treatment would take 25-30 minutes (several minutes per beam)
- Not compatible with DIBH
- Mean heart dose ~5-6Gy for left sided patients

Figure: Morganti et al. J App Clin Med Phys 2011.

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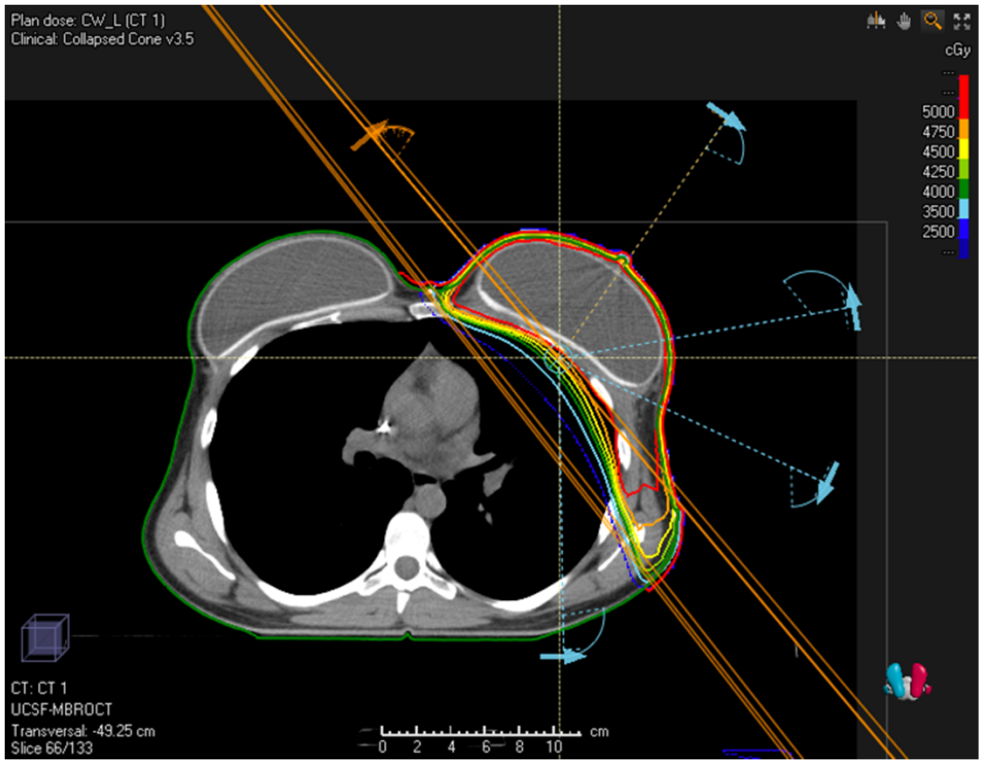
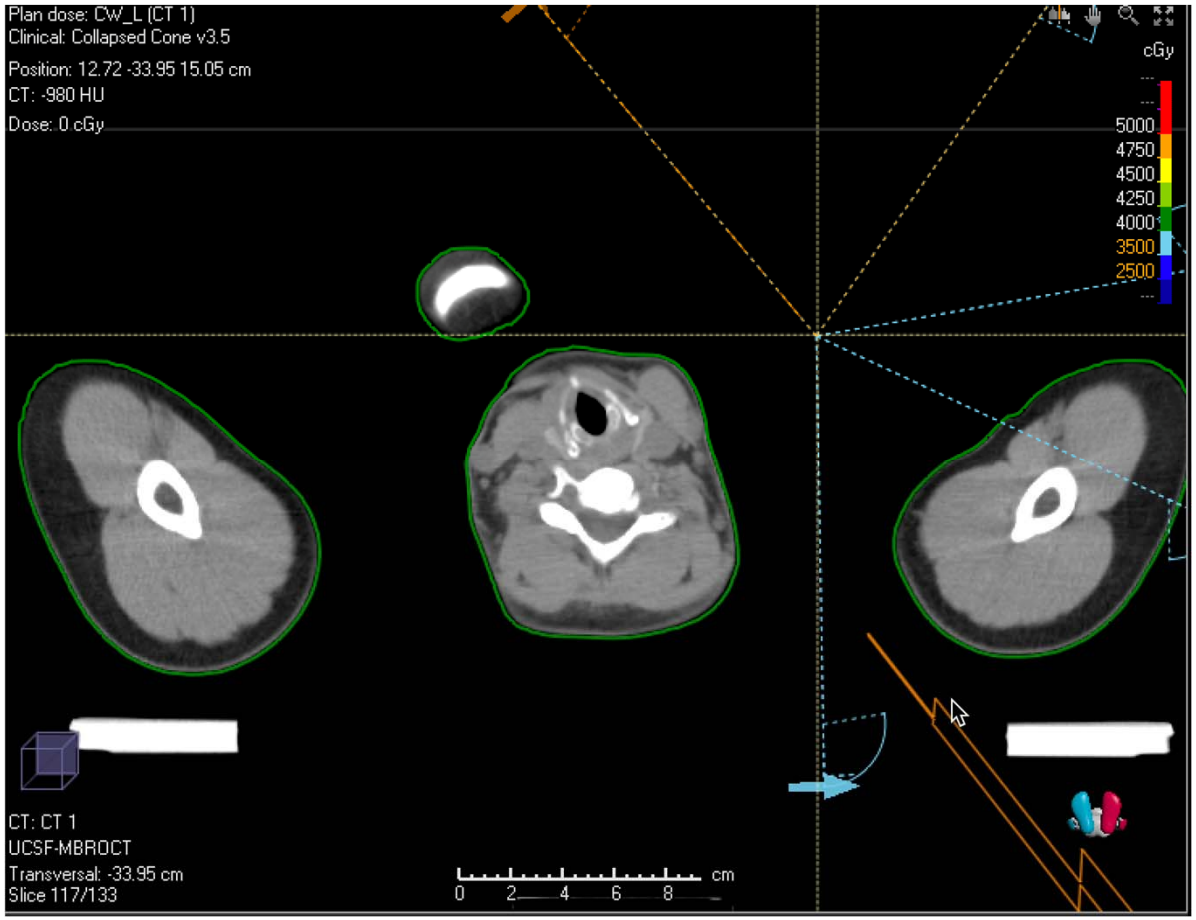
Transition from Static Beams to Arcs



- Generally, we use 3-5 arcs
- Each arc can be delivered in 45-60 seconds
- Compatible with DIBH



Mean Heart Dose
2.96 Gy

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Take Home Points

1. Cardiac toxicity from radiation therapy is related to **dose**.

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2. Modern radiation therapy for early-stage breast cancer ensures that the heart receives a **minimal dose**, at levels that do not (or barely) increase risk of cardiac toxicity.

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3. **DIBH** is an excellent way to minimize heart exposure during left sided breast radiation.

Take Home Points

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2. Modern radiation therapy for early-stage breast cancer ensures that the heart receives a **minimal dose**, at levels that do not (or barely) increase risk of cardiac toxicity.

3. **DIBH** is an excellent way to minimize heart exposure during left sided breast radiation.

4. In patients with left sided breast cancer who require regional nodal irradiation, **IMRT** can reduce heart dose and **VMAT with DIBH** can further minimize heart exposure

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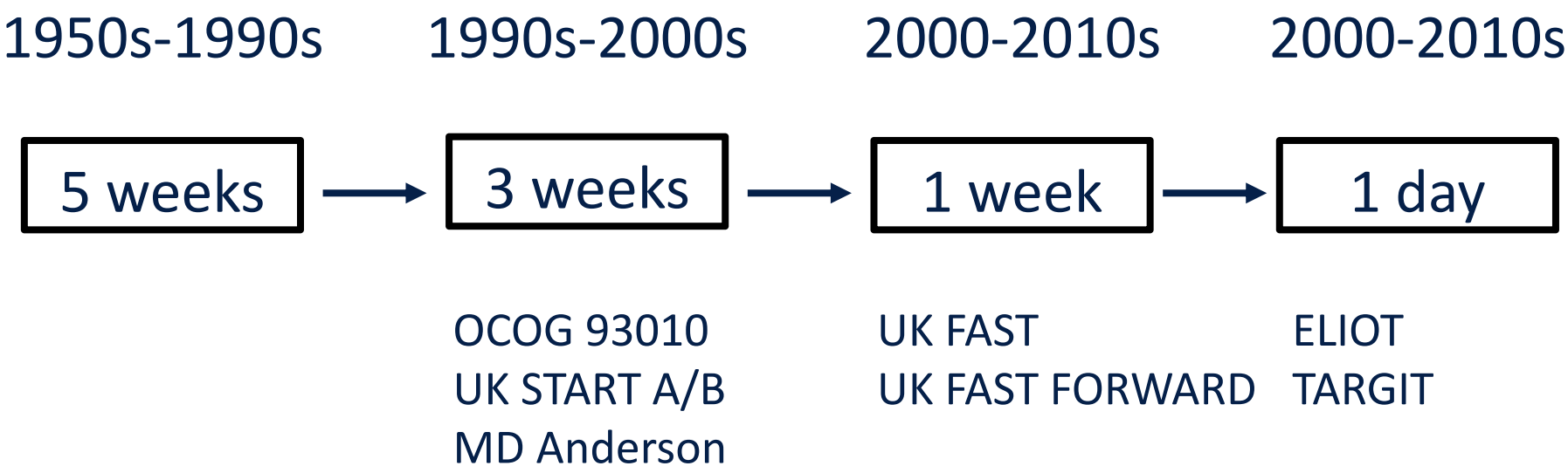
Moving Towards Shorter Treatment Courses

Nicolas Prionas MD PhD

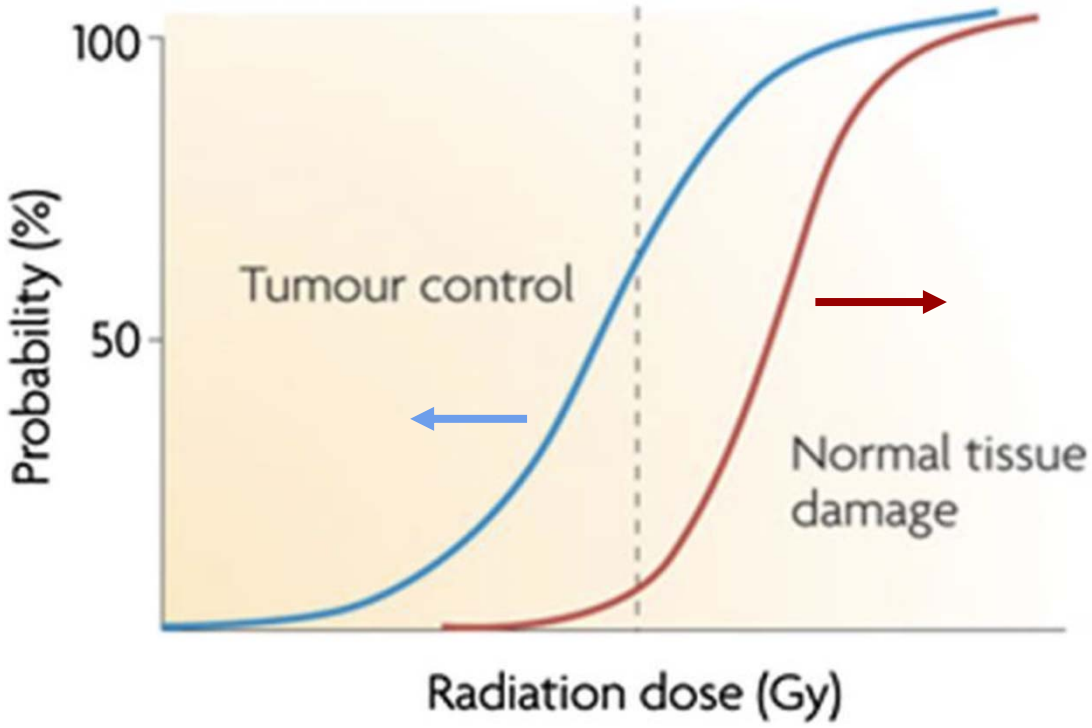
Learning Objectives

- Describe the ways in which new technology can help us to better protect the heart during radiation therapy for breast cancer
- **Understand the stepwise progress towards shorter courses of treatment for breast cancer patients**
- Become familiar UCSF's unique approach towards skin care in breast cancer patients

Less is more: trend toward shorter treatment



Therapeutic Ratio and Hypofractionation



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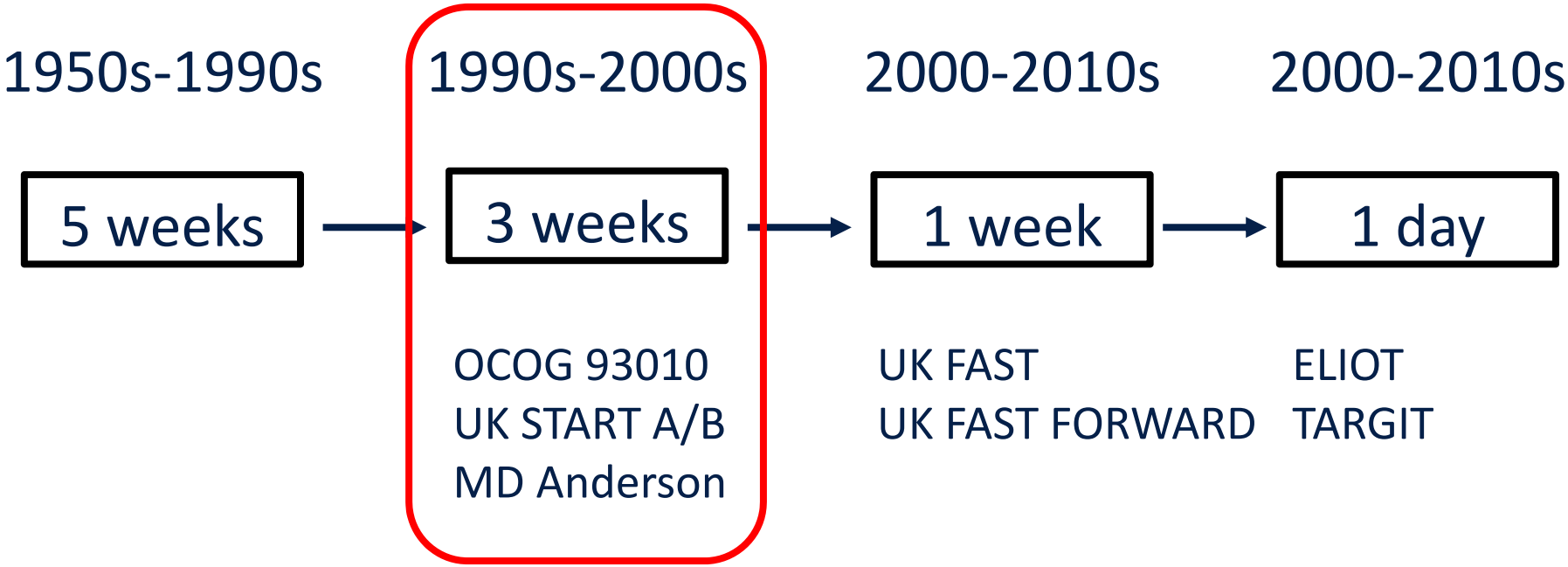
Ray, K J et al. “Treatment of Breast and Prostate Cancer by Hypofractionated Radiotherapy: Potential Risks and Benefits.” *Clinical oncology (Royal College of Radiologists (Great Britain))* vol. 27,7 (2015): 420-6

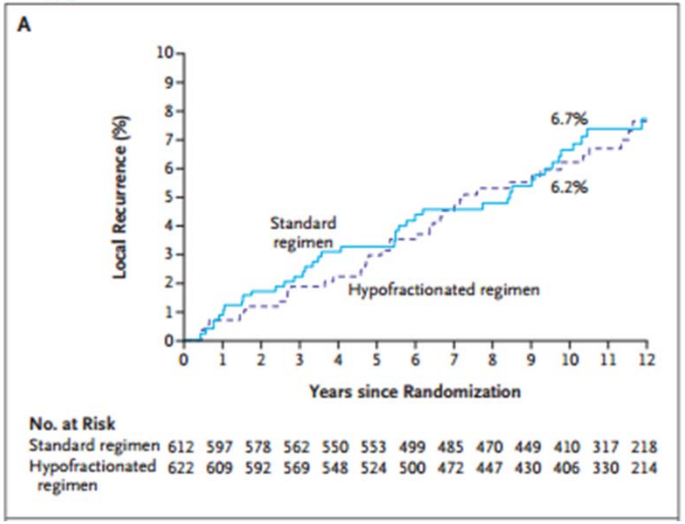
Trial	Total Dose (Gy)	Fractions	Dose/fx (Gy)	EQD2(α/β=3)
	50	25	2	50
Canadian	42.56	16	2.66	48.2
UK START B	40.05	15	2.67	45.4
UK FAST	28.5	5	5.7	49.6
UK FAST FORWARD	26	5	5.2	42.6

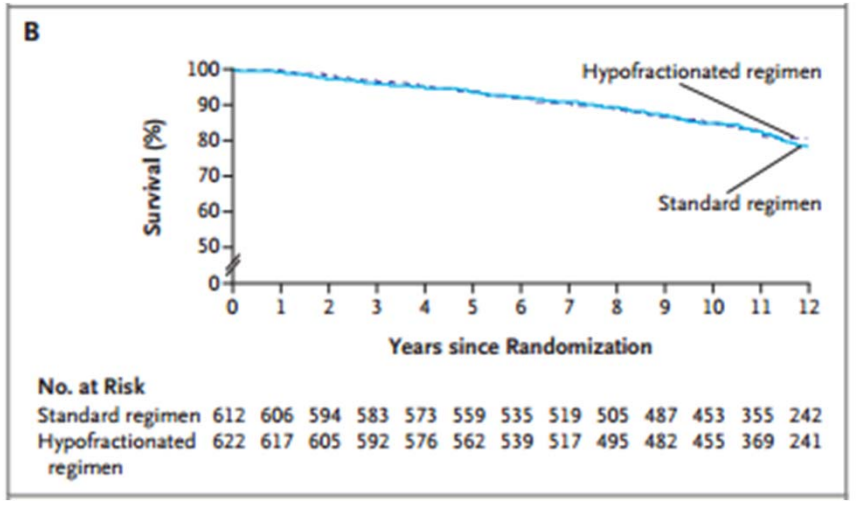
Less is more: trend toward shorter treatment



Canadian Hypofractionation (OCOG 93010)

- 1234 women, T1-2N0, lumpectomy + ALND, separation <25 cm
- 42.5 Gy/16 fx vs 50 Gy/25 fx (no boost)
- No difference in local recurrence, disease-free survival, or cosmesis @10 yr





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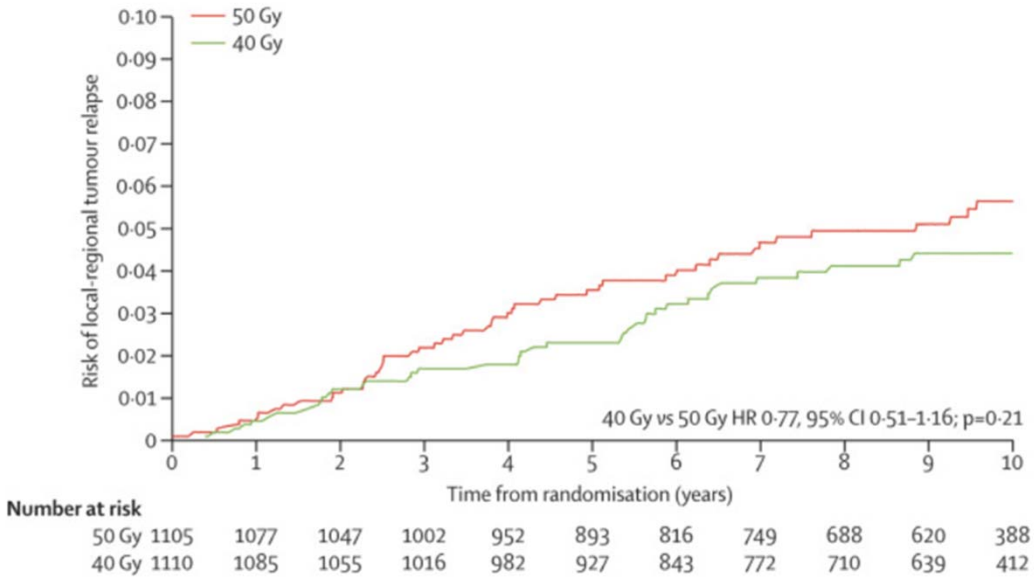
Whelan et al. JNCI 2002, NEJM 2010.

UK START B

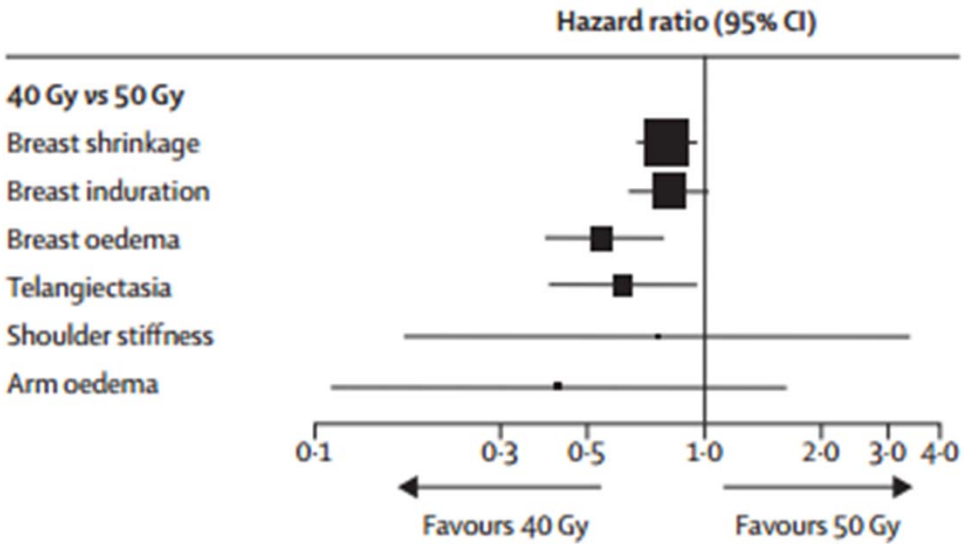
- 2215 women, pT1-3N0-1
- 40 Gy/15 fx vs 50 Gy/25 fx (optional 10 Gy boost, 43%)



Haviland et al. Lancet Onc. 2013.

UK START B

- Physician assessed cosmesis



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Haviland et al. Lancet Onc. 2013.

MD Anderson Hypofractionation

- Patients who were not well represented on other trials
  - N=287
  - 76% overweight or obese
  - 79% C cup or larger

- 42.5 Gy/16 fx vs 50 Gy/25 fx + boost

- Hypofractionation had less dermatitis, pruritus, breast pain, fatigue, lack of energy and trouble meeting family needs (@ 6 months)

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Shaitelman SF et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. *JAMA Oncol.* 2015;1(7):931–941

Hypofractionation - ASTRO Consensus

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

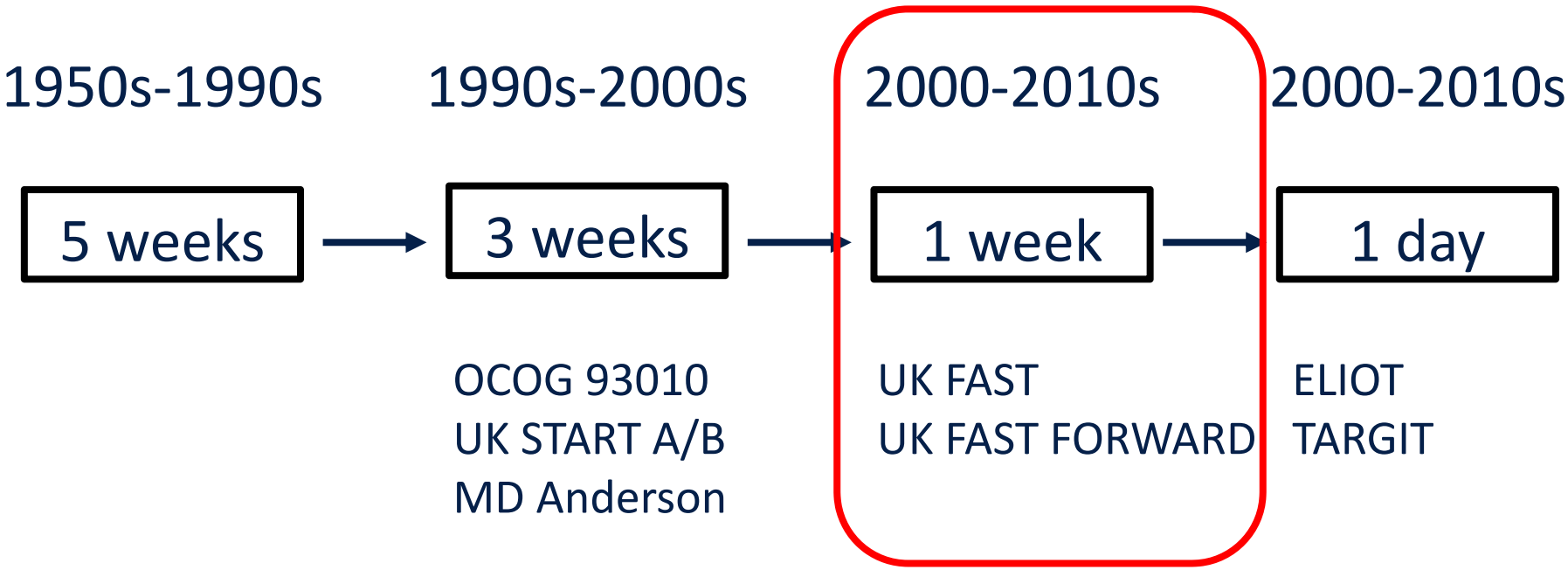
Practical Radiation Oncology (2018)

Radiation Therapy for the Whole Breast: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline

Statement KQ1A: For women with invasive breast cancer receiving WBI with or without inclusion of the low axilla, the preferred dose-fractionation scheme is HF-WBI to a dose of 4000 cGy in 15 fractions or 4250 cGy in 16 fractions.

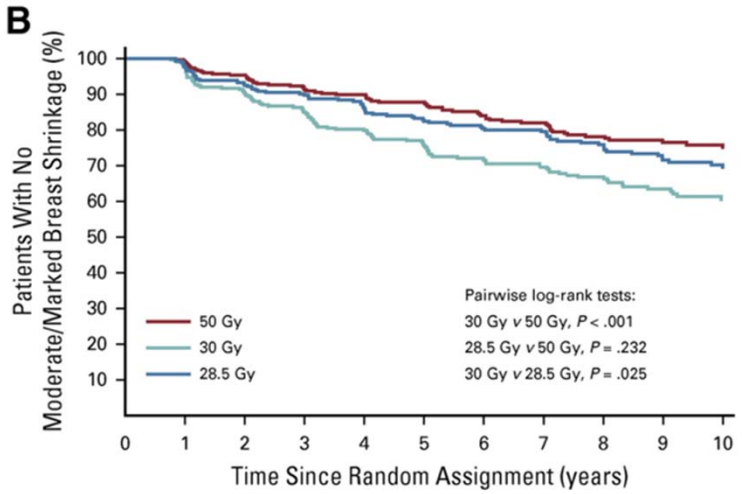
- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 100%

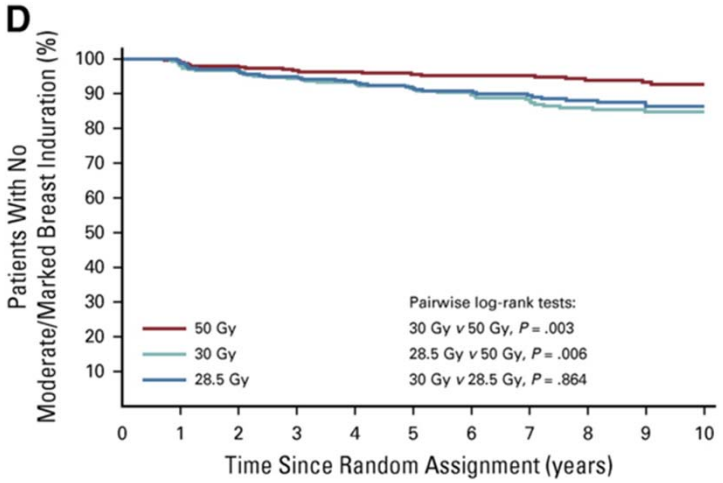
Less is more: trend toward shorter treatment



UK FAST

- >50 yo, T1-2 (<3 cm), N0
- N=915
- 28.5 Gy or 30 Gy/5 fx (once weekly) vs 50 Gy/25 fx





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FAST Trialists group, Brunt AM et al. Journal of Clinical Oncology 38, no. 28 (October 01, 2020) 3261-3272.

UK FAST

TABLE 5. Survival Analysis of Ipsilateral Disease in the Breast Overall and by Fractionation Schedule

Fractionation Schedule	Ipsilateral Breast Event[a]/Total (%)	KM Estimate (95% CI) of Cumulative Incidence (%)		Hazard Ratio (95% CI)
		5 Years	10 Years	
All patients	11/915 (1.2)	0.7 (0.3 to 1.6)	1.3 (0.7 to 2.3)	—
50 Gy	3/302 (1.0)	0.7 (0.2 to 2.8)	0.7 (0.2 to 2.8)	1
30 Gy	4/308 (1.3)	1.0 (0.3 to 3.2)	1.4 (0.5 to 3.8)	1.36 (0.30 to 6.06)
28.5 Gy	4/305 (1.3)	0.4 (0.05 to 2.6)	1.7 (0.6 to 4.4)	1.35 (0.30 to 6.05)

Abbreviation: KM, Kaplan-Meier.

[a]Includes 1 patient with angiosarcoma in the ipsilateral breast (30 Gy).

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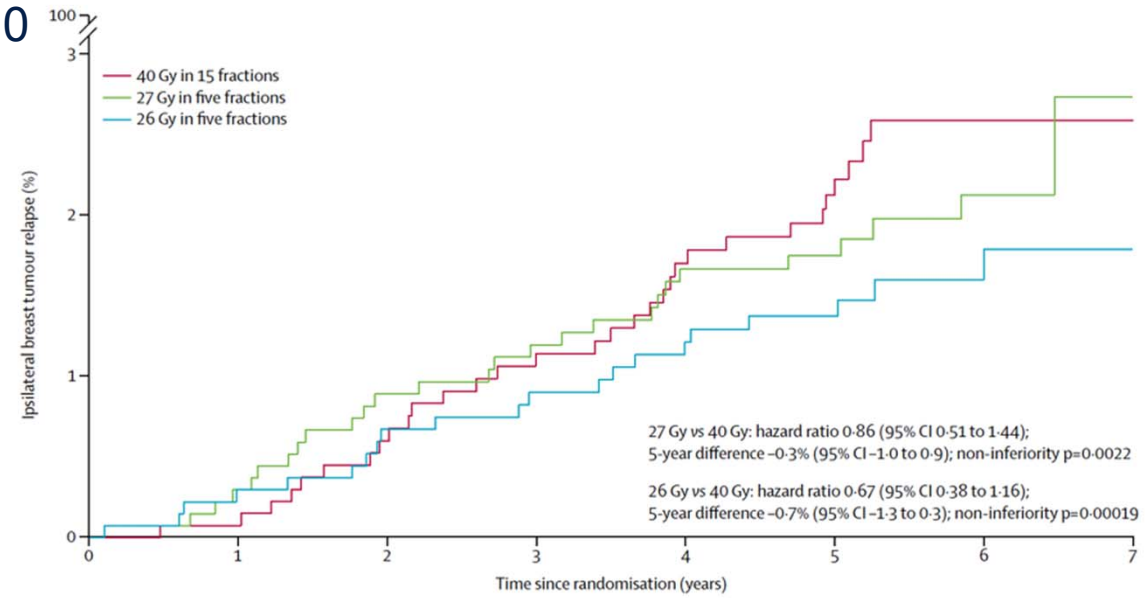
FAST Trialists group, Brunt AM et al. Journal of Clinical Oncology 38, no. 28 (October 01, 2020) 3261-3272.

UK FAST FORWARD

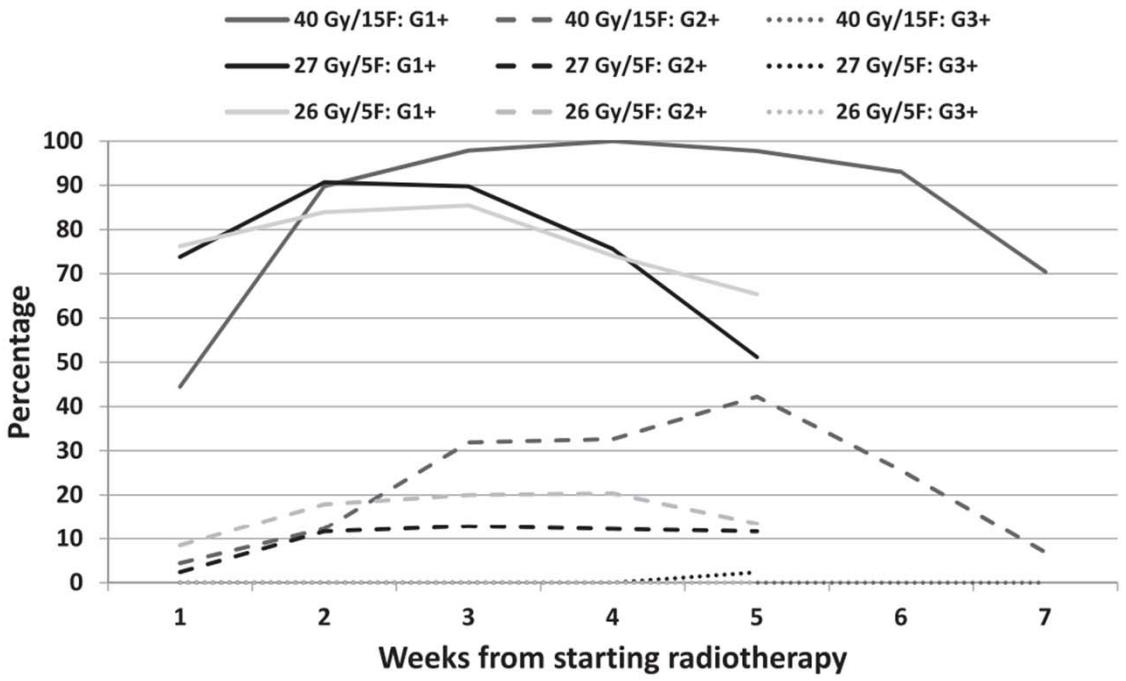
- >50 yo, T1-2 (<3 cm), N0
- N=190 + 162
- 40 Gy/15 fx vs

  27 Gy or 26 Gy/5 fx (one week)



FAST Trialists group, Agrawal RK et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol. 2011 Jul;100(1):93-100.

UK FAST FORWARD



Grade 3 toxicity reported at 4 weeks post-RT in 27 Gy/5F patient resolved to grade 1 one week later

❿ At 5 years

- Increased induration (1.6 vs 0.8%)
- Increased edema (2.4 vs 1.5%)

Brunt AM et al. FAST-Forward Trial Management Group. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol. 2016 Jul;120(1):114-8.

Hypofractionated PMRT – Chinese trial

- Post-mastectomy, T3-4N2-3 (N=820)
- Arms
  - Conventional (50 Gy / 25 fx)
  - Hypofx (43.5 Gy / 15 fx)
- Median follow-up 58.5 months
- 5-year local recurrence (8.3 vs 8.1%)
- No difference in overall toxicity
  - Except less acute grade 3 skin toxicity (8 vs 3%)

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Acute toxicity			
Skin toxicity	..	..	<0·0001
Grade 1–2	357 (87%)	351 (89%)	..
Grade 3	32 (8%)	14 (3%)	..
Pneumonitis	..	..	0·278
Grade 1	62 (15%)	61 (15%)	..
Grade 2	7 (2%)	14 (3%)	..
Grade 3	..	..	..
Late toxicity			
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

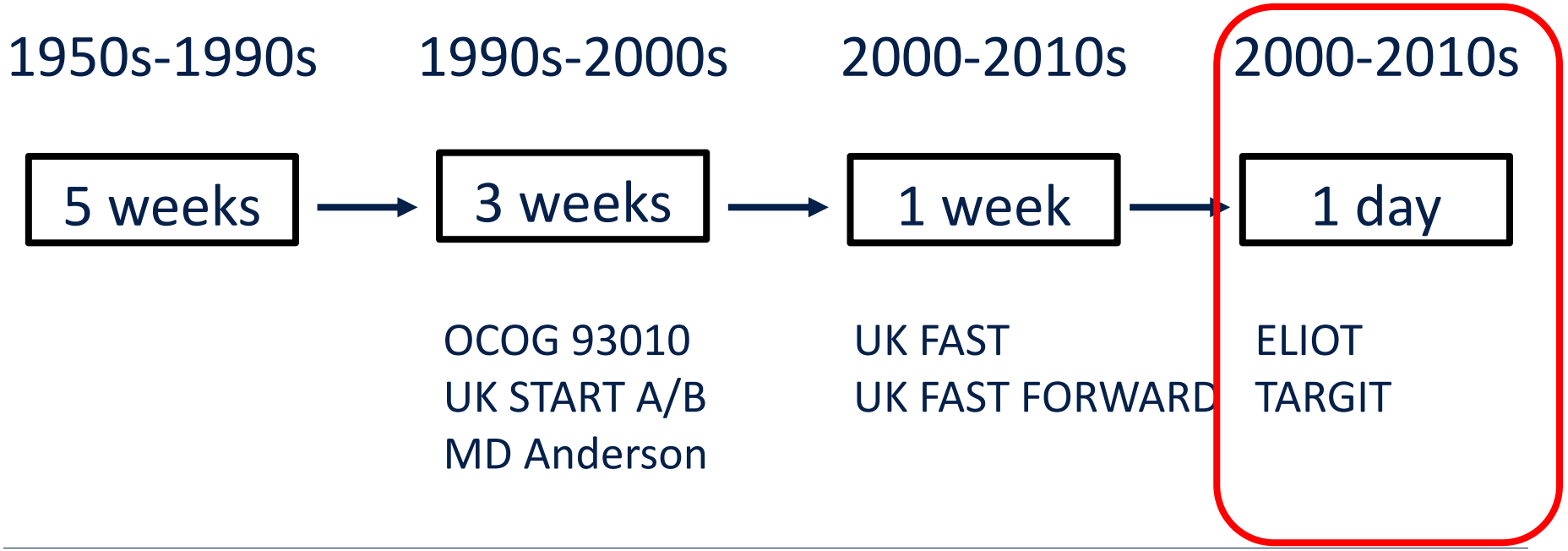
Data are n (%). The χ^2 test was used to calculate p values. No grade 4 events or deaths due to adverse effects were reported.

Table 2: **Adverse events**

Hypofractionated PMRT after implant reconstruction

- FABREC Trial - Currently accruing
- T1-3N+
- Arms
  - Conventional: 50 Gy / 25 fx
  - Hypofractionated: 42.56 Gy / 16 fx (39.9 Gy / 15 fx to SCV)
- Outcome measures
  - Primary: patient reported, 6 month physical well being
  - Secondary: Oncologic, clinical, and cosmetic

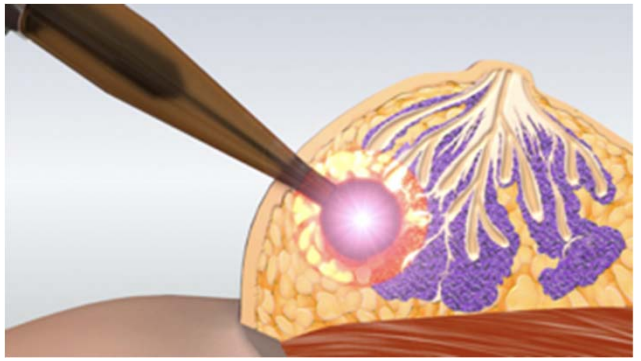
Less is more: trend toward shorter treatment



Intraoperative radiation - ELIOT trial

TARGIT Trial

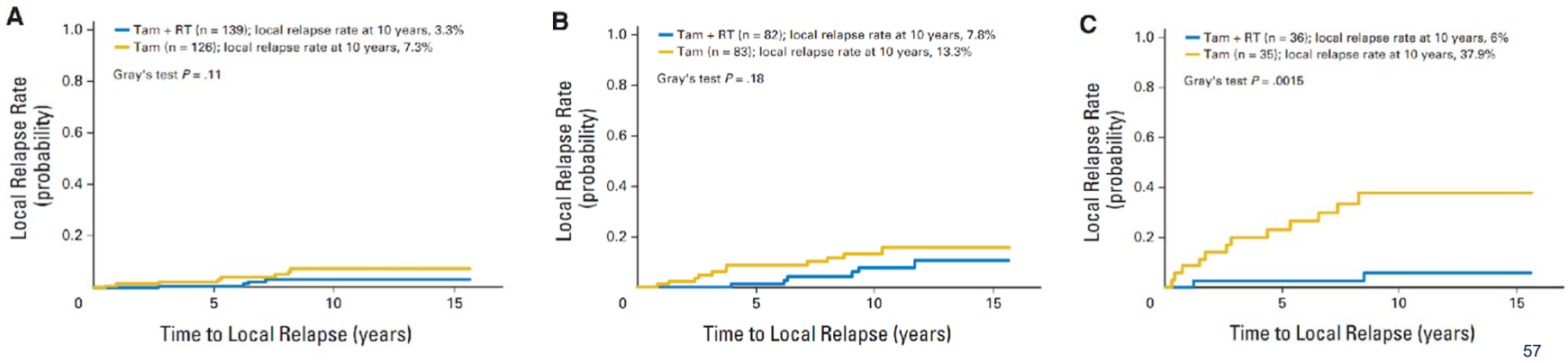
- >45 yo, <2 cm, grade 1-2, N0, ER/PR+
- Hypofx WBRT vs 20 Gy orthovoltage IORT (+/- optional WBRT)
- 5 yr LR: 3.3% (IORT) vs 1.3% (WBRT)
- IORT had better toxicity, cosmesis, QoL
- Decreased cardiac deaths with IORT



ELIOT Trial

- >48 yo, <2.5 cm
- WBRT (50 Gy/20 fx + boost) vs 21 Gy electron IORT (to 90%)
- 5 yr LR: 4.4% (IORT) v 0.4% (WBRT)
- IORT had less skin toxicity

Low-risk breast cancer histology



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Luminal A (ER+, low Ki67)

Luminal B (ER+, high Ki67)

HER2(+)/Basal-like (Triple negative)

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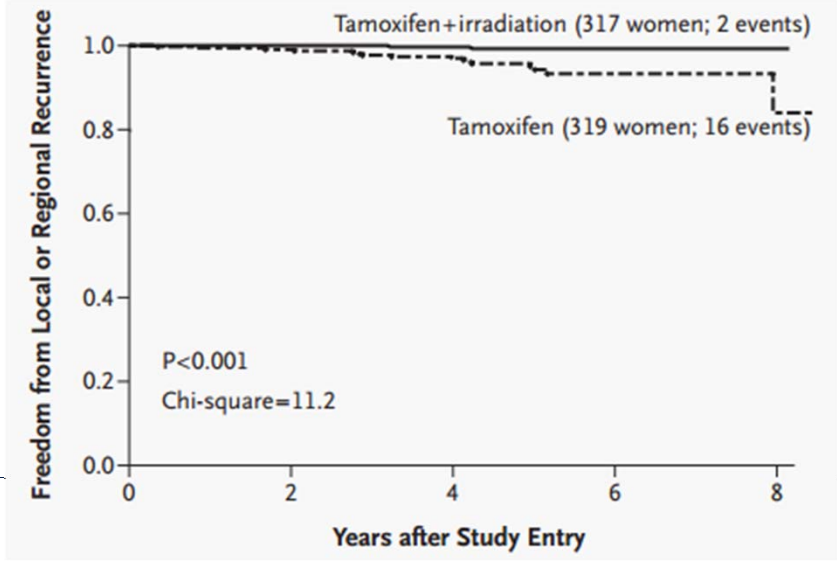
Liu et al. JCO 2015.

Omission of radiotherapy - CALGB 9343

- ≥70 yo, T1, cN0, ER+, lumpectomy, margins-
- N=636 women
- Tamoxifen vs tamoxifen + RT (45 Gy + 14 Gy boost)



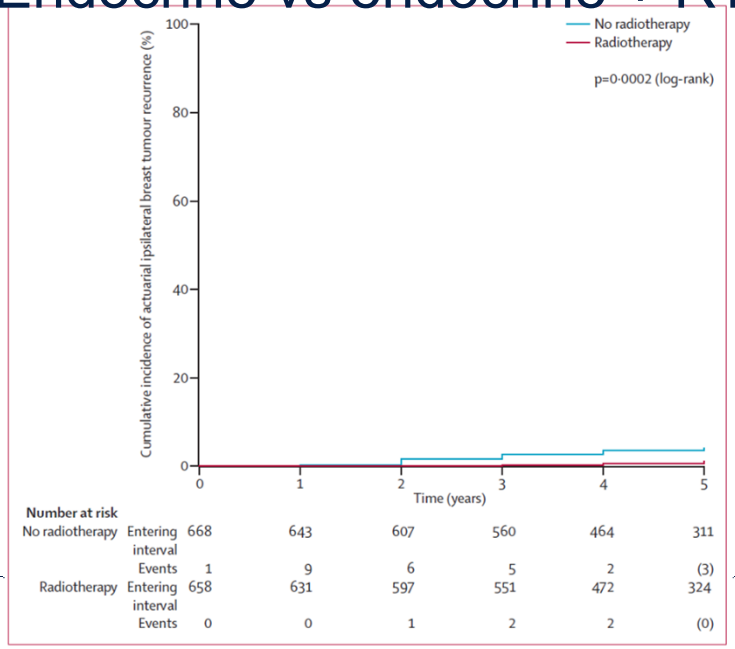
@ 10 yrs	Tamoxifen	Tamoxifen + RT
LR	10%	2%
OS	66%	67%

No difference in time to mastectomy, DM, DSS, or OS.

Hughes et al, NEJM 2004, JCO 2013

Omission of radiotherapy - PRIME II

- ≥65 yo, ≤ 3 cm, pN0, ER+, lumpectomy, margins-
- N=1326 women
- Endocrine vs endocrine + RT (40-50 Gy + 14 Gy boost)



@ 5 yrs	Tamoxifen	Tamoxifen + RT
LR	4.1%	1.3%
OS	93.9%	93.9%

Kunkler et al, Lancet Oncol 2015

Consideration of omission of adjuvant XRT

>65 years old

ER+ (with plan for hormone therapy)

T1N0 (<3 cm)

Negative surgical margins

UCSF

University of California
San Francisco

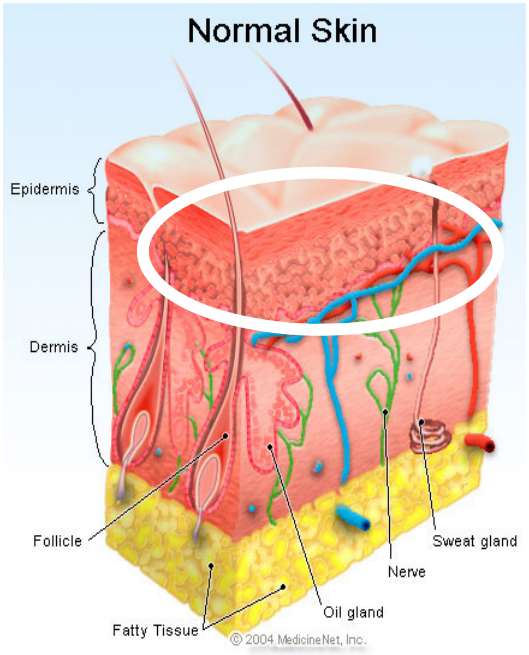
"It's Not a Sunburn!" Our Approach to Skin Care for Breast Cancer Patients

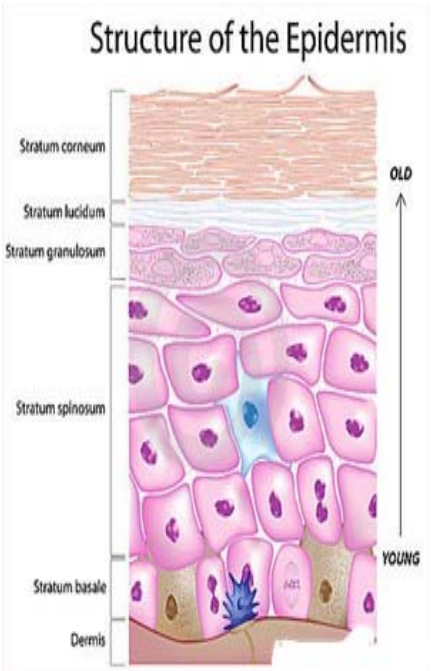
Florence Yuen RN MSN AOCNP

Learning Objectives

- Describe the ways in which new technology can help us to better protect the heart during radiation therapy for breast cancer
- Understand the stepwise progress towards shorter courses of treatment for breast cancer patients
- **Become familiar UCSF's unique approach towards skin care in breast cancer patients**

Acute Radiation Dermatitis
90% of our patients will develop it





Grading Radiation Reactions
RTOG or CTCAE

0 No reaction

1 Faint erythema, follicular reaction, dry desquamation, epilation, diminished sweating.

2 Tender or bright erythema

2.5 Patchy moist desquamation/edema

3 Intense edema, confluent moist desquamation, other than skin folds, pitting edema.

4 Ulceration, hemorrhage, necrosis

Radiation Reactions: Contributing factors

- Cumulative dose (anything above 30 Gy)
- Dose per fraction (length of treatment)
- Proximity of sensitive tissues and organs (SCV)
- Surgery (BCS/Mastectomy/Mastectomy with reconstruction)
- Use of bolus
- Concurrent therapy (Xeloda)
- Individual patient characteristics (Weight/Breast size/skin tone/age)
- Boost (extra dose to the lumpectomy cavity or active tumor nodules—targeted 1000 to 1250 cGy)

Radiation Dermatitis Timeline

- Weeks 1-2
  - Minimal skin reaction
  - Minimal to no discomfort
  - Beginning of hyperpigmentation and/or mild erythema may begin end of week 2 (rarely)

- Weeks 3-4
  - May experience dryness and puritis (decreased functioning of the sweat and sebaceous glands)
  - Mild Erythema
  - Discomfort mild to increasing, skin may feel sensitive

Radiation Dermatitis Timeline

- Weeks 4 - 6
  - Moderate to severe erythema
  - Dry desquamation peeling/flaking of the skin
  - Hyperemia and edema(extra-capillary cell damage with increased capillary blood flow
  - Moist desquamation (exposed dermis, moist, tender, serous exudate)
  - Increased discomfort

Types of Acute Reactions

Mild Erythema

Moderate Erythema

Infected Moist Desquamation

Resolving Moist desquamation

Dry Desquamation

Hyperpigmentation

UCSF

Standard Skin Care: 5 weeks 50 Gy

Cleansing and moisturizing

Push to do better!

General Skin Guidelines

No Standard of Care

- Wash with mild soap and water
  - ➉ Dove, Neutrogena, cetaphil, **skintegrity spray**
- Pat the skin dry
  - ➉ No rubbing, No wash cloths, no exfoliation
- Avoid irritants (alcohol, gels, lanolin, tea tree oil)
- NO TAPE
- Protect the skin from sun and friction
- Deodorant/Antiperspirant use ALLOWED
- Moisturizers recommended

Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Group (Multinational Association For Supportive Care in Cancer 2013)

Helpful

- High potency topical Steroid cream (Mometesone)
- Mepitel film showed to deter moist desquamation

Not Recommended

- Aloe
- Oils

No Difference

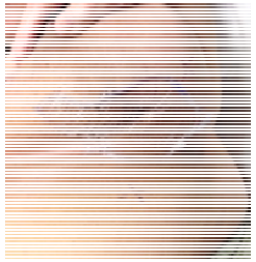
- Biafine
- Calendula Cream +/- (Insufficient evidence)

UCSF Breast Service standard skin care

- Cleansing
- Moisture Management
- Management of desquamation
- Reduction of friction

Mepitel Film

5 Weeks 50 Gy

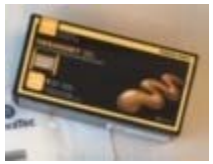


Replace every 7 to 10 days
Leave in place if it not lifting
Should be smooth with no bubbles
Teach them how to remove it
Remove if mod erythema or rash develops beneath
No other skin care required to the covered area

Mometesone 0.1%
Hypo-fractionation 40 Gy
Alternative to Mepitel

Mometesone daily (pm)/calendula (day)and skintegrity spray
Start of treatment and 1 week post (week 4)

Leptospermum Scoparium
"Manuka" Honey"

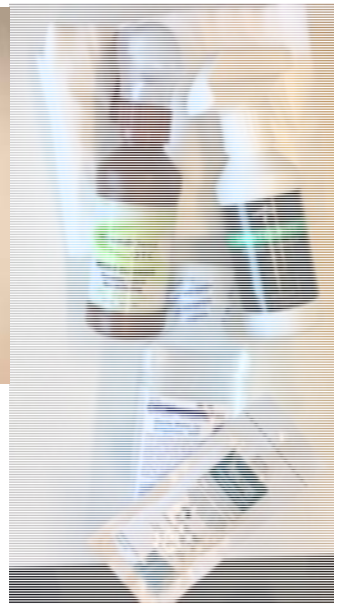


- Originated in New Zealand and Australia
- Methylglyoxal (MG) provides anti-bacterial effect.
- low pH and high osmolarity hinders microbe growth
- Facilitates wound hydration and moist healing wound environment
- Autolytic debridement
- Reduces biofilm
- Antibacterial effect against gram-positive, gram-negative, anaerobic and MRSA
- Humectant

Silicone Dressings
Mepilex Lite

- Adheres to healthy skin but not to open wounds—minimizing trauma to the skin
- Safetach technology
- Remove mepilex lite during radiation treatments as they will cause a small bolus effect (0.5mm)
- Mepitel film minimal bolus

Management of Moist Desquamation
Out with the old…….In with the new



Replacements:
Gauze & Tape → *Silicone dressings/hydrogels*
Silvadene → *Silver Ion dressings or hydrogel*
Triple antibiotic ointment → *Manuka Honey*

Vigilant skin care and follow up

~15% risk for implant loss

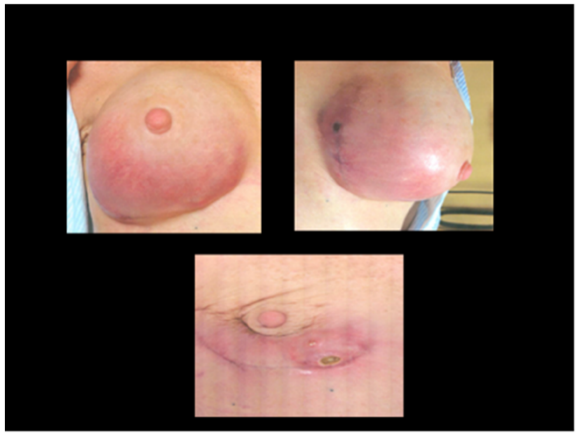
RECONSTRUCTION

Reconstruction: Complications

Early Cellulitis post radiation

Expander Extrusion

Infection and poor wound healing at time of exchange



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Thank You for Joining Us!

UCSF
University of California
San Francisco

Close to the Heart

Modern Radiation Therapy for Breast Cancer Treatment

Joanna C. Yang MD MPH
Nicolas Prionas MD PhD
Florence Yuen RN MSN AOCNP

10/22/2020