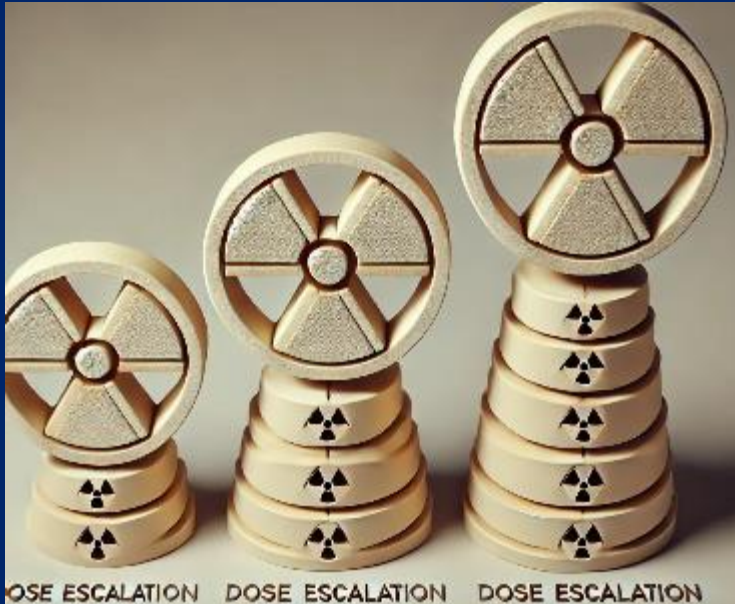


Radiation Dose Escalation for Breast Cancer

2024 Breast Cancer Symposium



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Memorial Sloan Kettering
Cancer Center



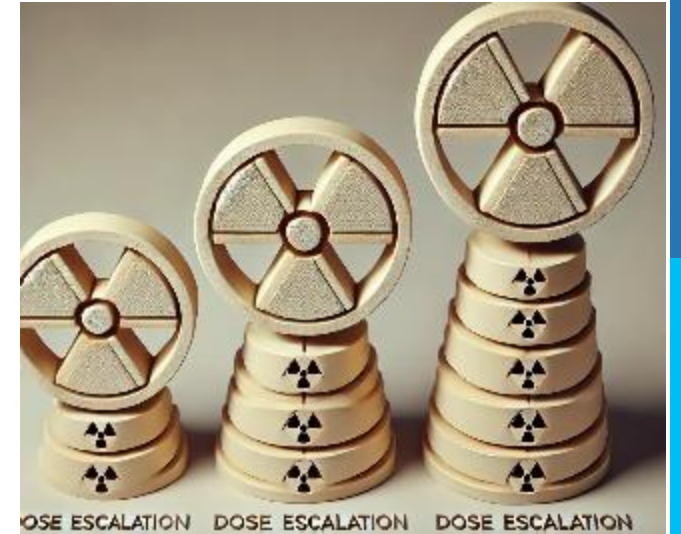
Dose Escalation Talk Overview

Common Topics in Escalation

- RT for Breast Cancer
- NCCN
- RT DOSE: Lumpectomy Cavity Boost Dose and SIB
- Faster RT – UK Fastforward & Florence PBI Trials
- RT Volume for N1 Disease

Future/Challenging Topics

- Re-RT Considerations
- RT for Gross Residual or Recurrent Disease
- Radiation Guided Nanoparticles

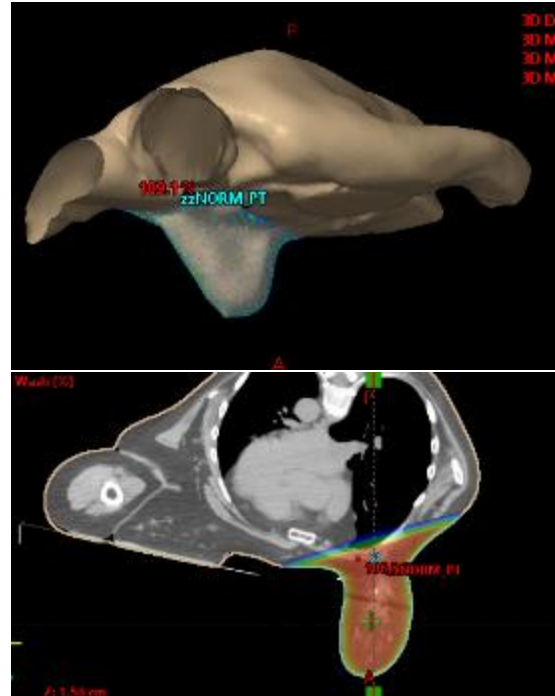


Radiation Therapy for Breast Cancer

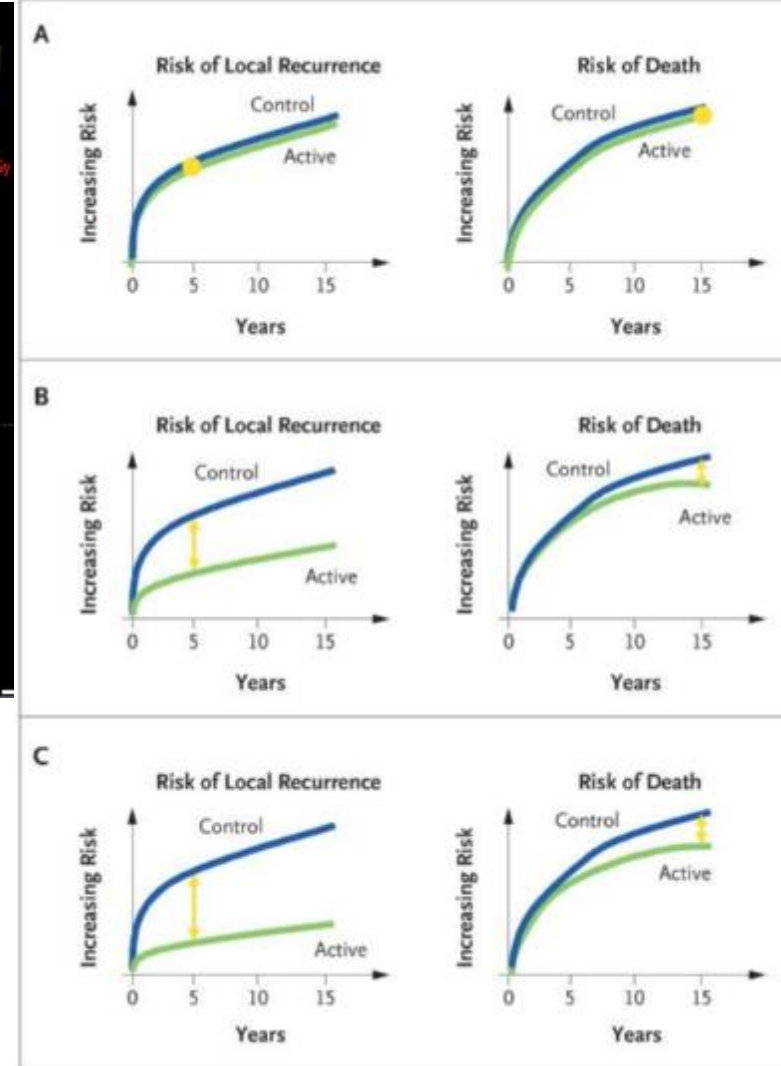
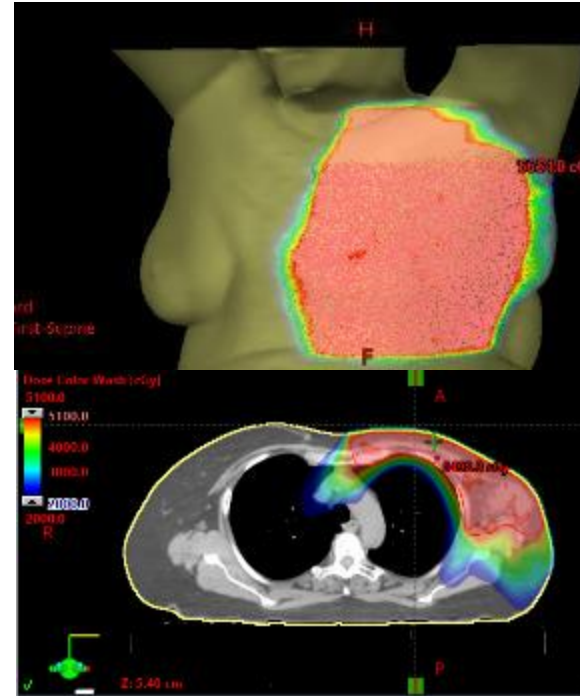
PBI



WBI



PMRT



Acute effects: Radiation Dermatitis, Fatigue, Pain

Late effects: Lymphedema, Limited Shoulder / Arm ROM, Adverse Cosmesis, Cardiac Disease, Brachial Plexopathy, Secondary Cancers

Other: Inconvenience, stress (psychosocial & financial)

Punglia et al, NEJM 2007

Early-stage breast cancer – locoregional management.

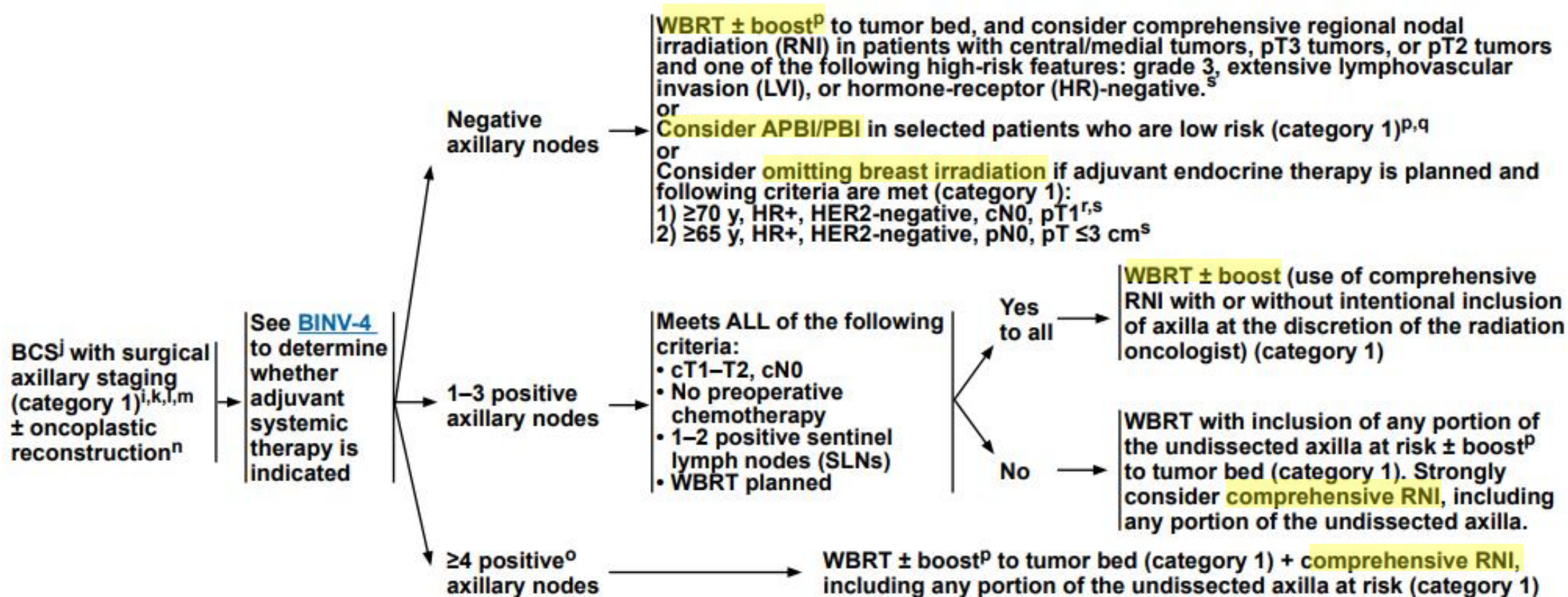


National
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NCCN Guidelines Version 4.2024 Invasive Breast Cancer

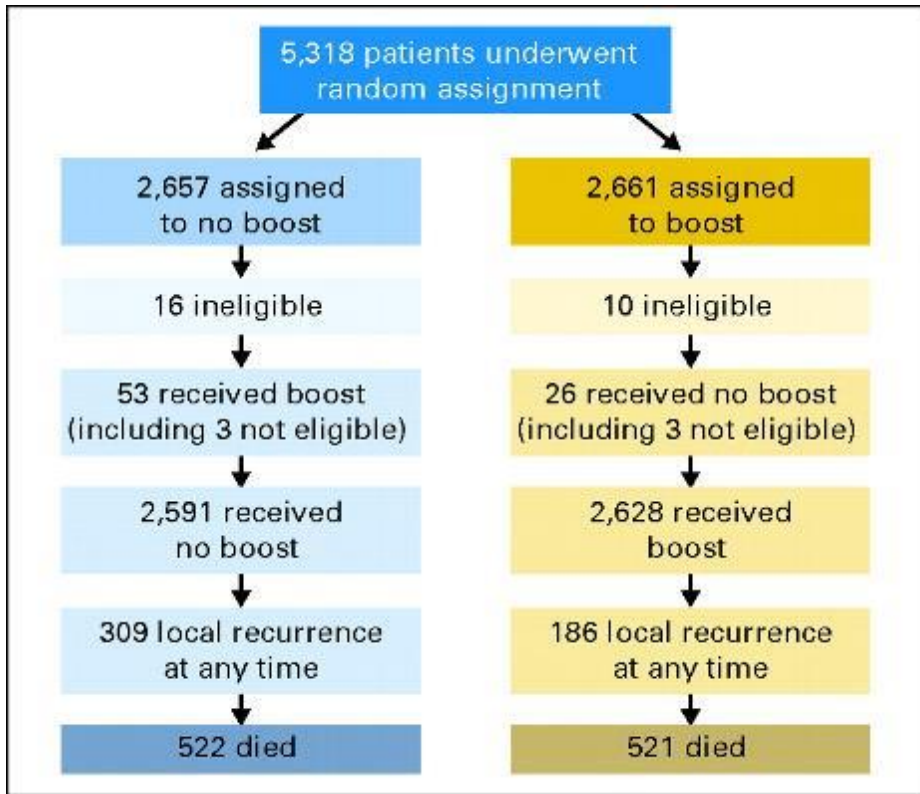
[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE^a: BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

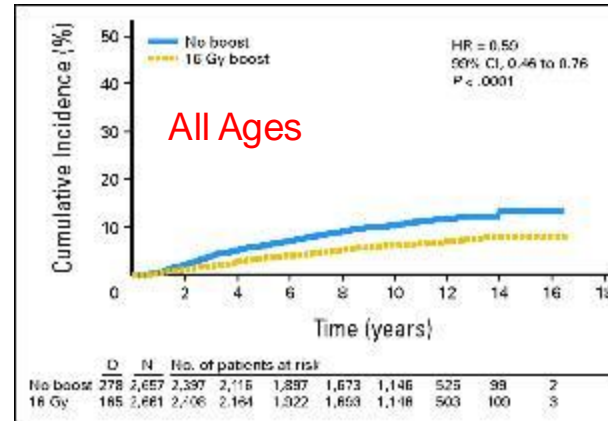


EORTC 22881 Boost Trial

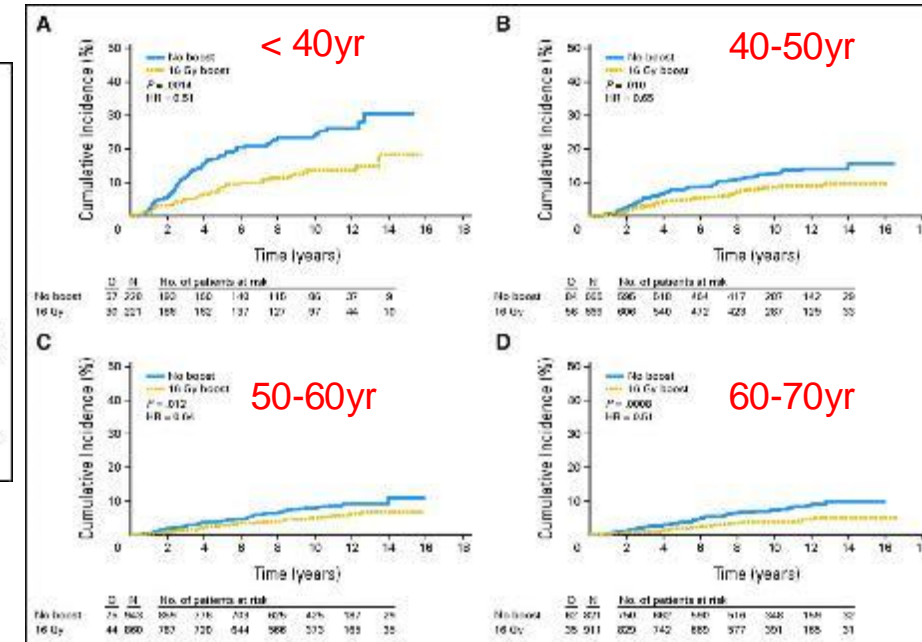
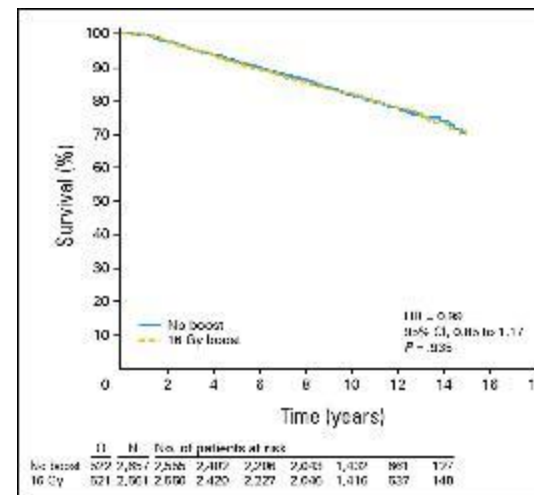
- 1989-1996. 5318pts, >18yr <70yr
- Post lump/ALND, pT1-2N0-1,
- plan for WBI (50/25fx)
- →randomized 16Gy Boost



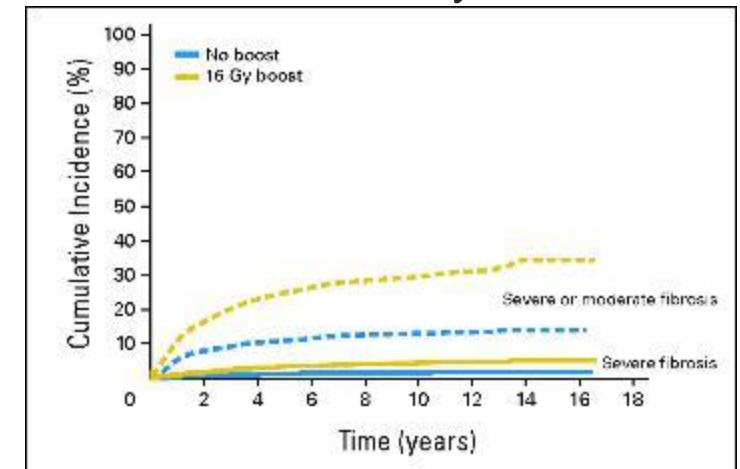
Local Control



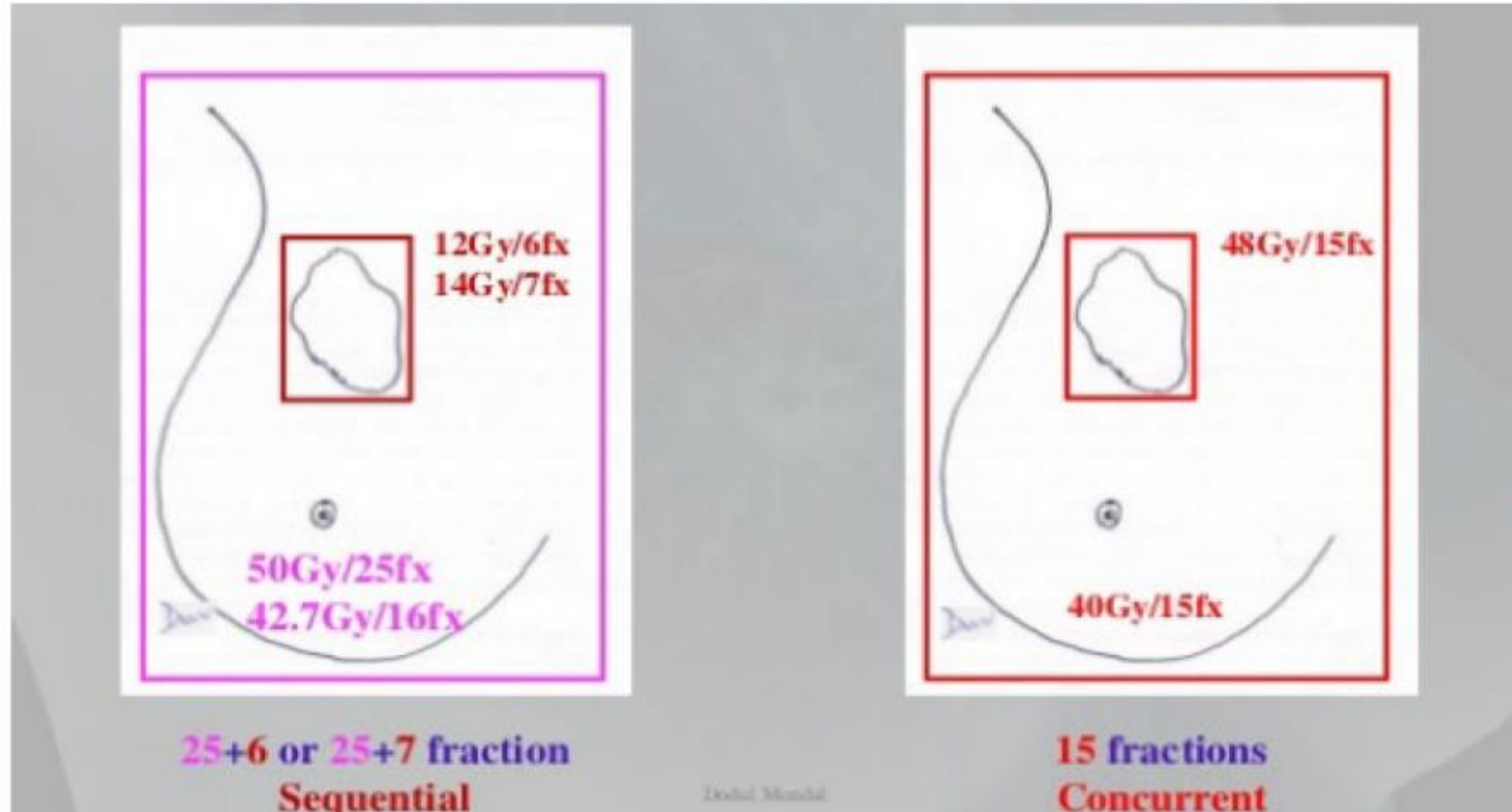
Survival



Toxicity



RTOG 1005: Concurrent Boost trial



TOTAL: 5-7 weeks RT

TOTAL: 3 weeks RT

RESULTS reported at ASTRO 2022

RTOG 1005: Concurrent Boost trial

Protocol-specified High Risk pts post L stages 0, I & II breast cancer

S		R	
T	Age < 50 vs. ≥ 50	A	
R	Chemotherapy Yes vs. No	N	ARM 1: Standard fractionation Whole Breast 50 Gy / 25 F or 42.7 Gy in 16 F Sequential Boost 12 Gy / 6 F or 14 Gy / 7 F
A	Histologic Grade 1, 2 vs. 3	D	
T	ER Status + vs. -	O	ARM 2: Hypofractionation (15 F total) Whole Breast 40 Gy/15 F/2.67 Gy daily Concurrent boost 48.0 Gy/3.2 Gy daily
I		M	
F		I	
Y		Z	
		E	

RTOG 1005: Patient and Tumor Characteristics

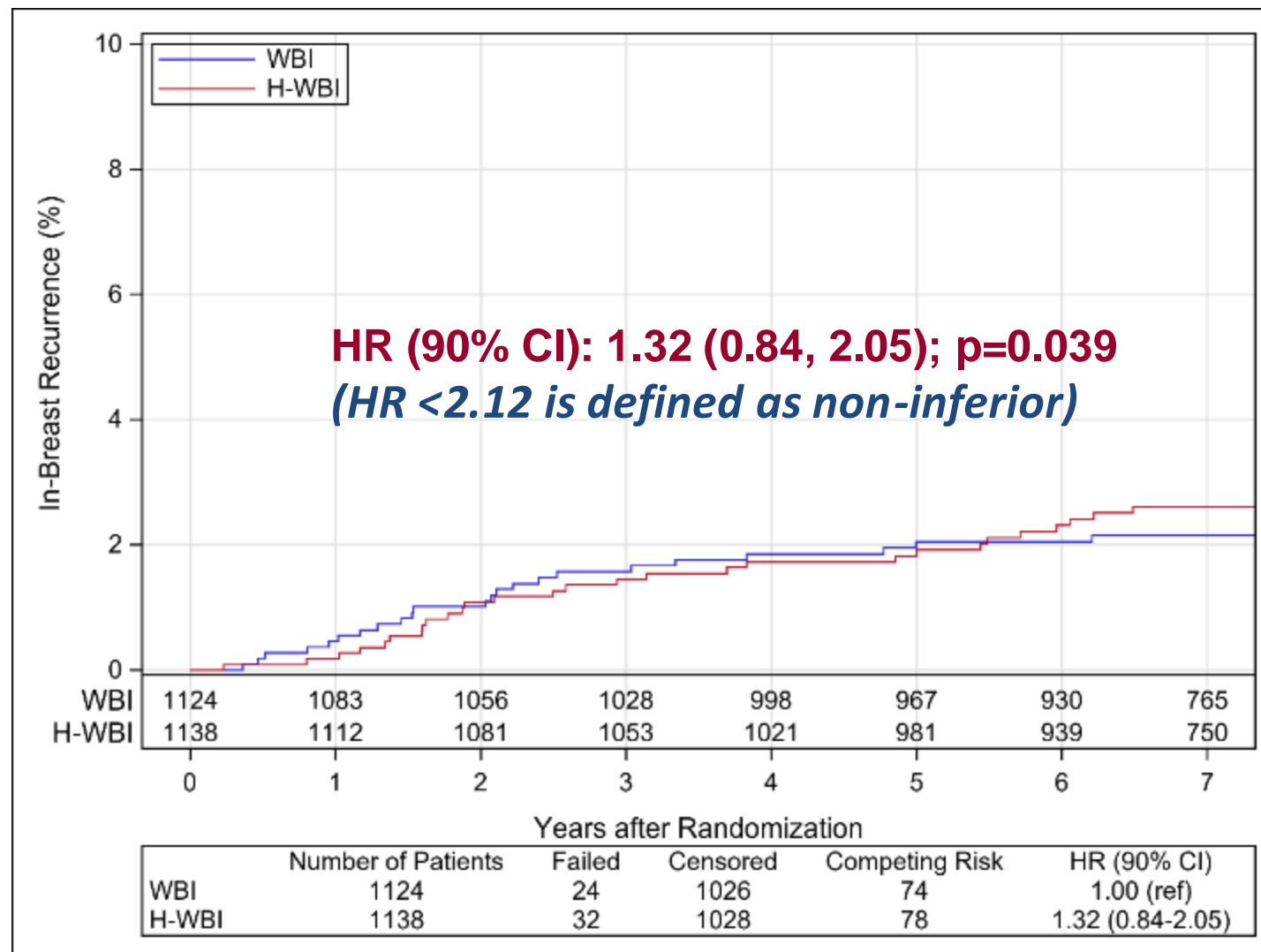
	WBI Sequential Boost (n=1124)	H-WBI Concurrent Boost (n=1138)
Median Age	55	55
< 50 years	403 (36%)	400 (35%)
Pathologic Stage II	399 (35%)	376 (33%)
Gr 3 histology	589 (52%)	593 (52%)
ER (-)	335 (30%)	350 (31%)
Close/(+) margins	182 (16%)	196 (17%)
Adjuvant Chemo	678 (60%)	697 (61%)
Gr 3 DCIS and <50 years	32 (3%)	31 (3%)

Results: Primary Endpoint - IBR

Median follow-up: 7.4 years

IBR events: 56

	WBI Sequential Boost (n=1124)	H-WBI Concurrent Boost (n=1138)
5-year estimate (90% CI)	2.0% (1.4%, 2.9%)	1.9% (1.3%, 2.7%)
7-year estimate (90% CI)	2.2% (1.5%, 3.0%)	2.6% (1.9%, 3.5%)
Median time to IBR	2.05 years	3.04 years

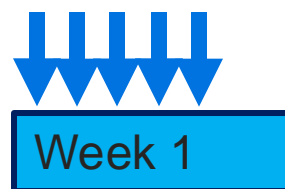
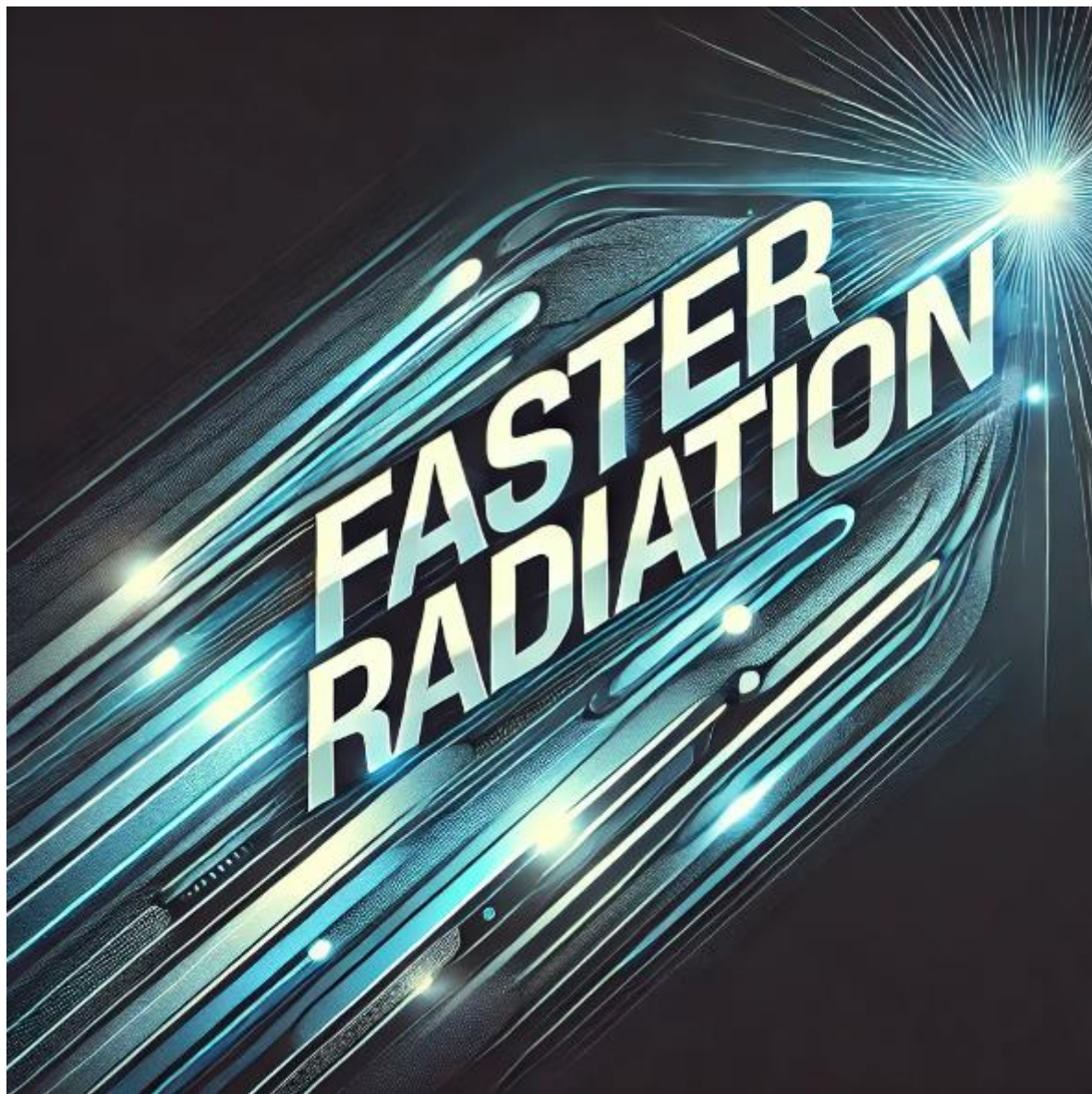


Results: Treatment-Related Adverse Events

Highest Grade Adverse Event Definitely, Probably, or Possibly Related to Protocol Treatment

	WBI Sequential Boost (n=1100)					H-WBI Concurrent Boost (n=1123)				
	n and % of Patients by Grade					n and % of Patients by Grade				
Overall Highest Grade	1	2	3	4	5	1	2	3	4	5
All	427 39%	379 34%	34 3%	2 <1%	0 0%	554 49%	290 26%	35 3%	4 <1%	0 0%
50 Gy / 25 F	210 37%	224 39%	22 4%	1 <1%	0 0%	-	-	-	-	-
42.7 / 16 F	217 41%	155 30%	12 2%	1 <1%	0 0%	-	-	-	-	-
Grade ≥ 3 (p=0.79)	36 (3.3%)					39 (3.5%)				

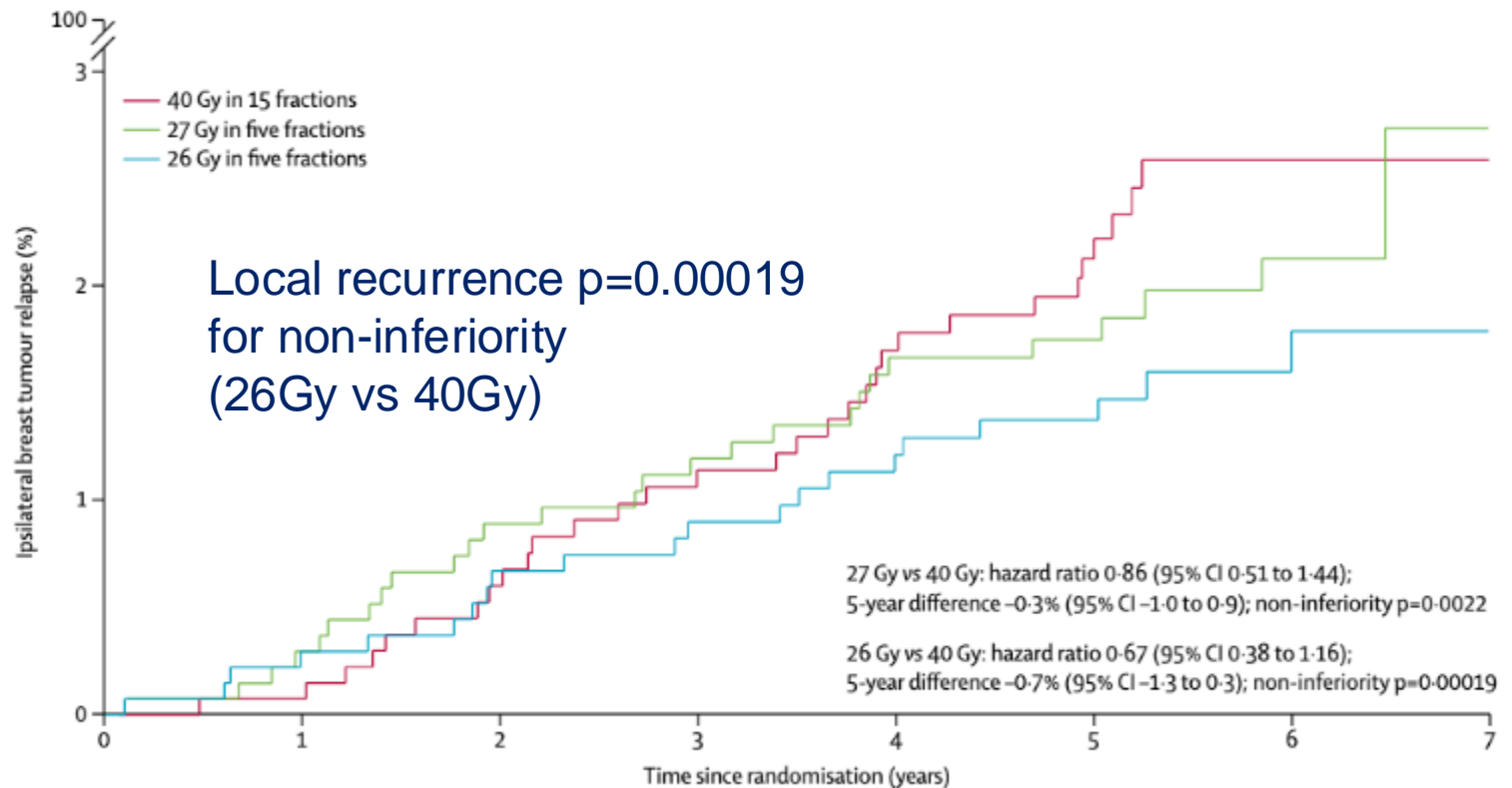
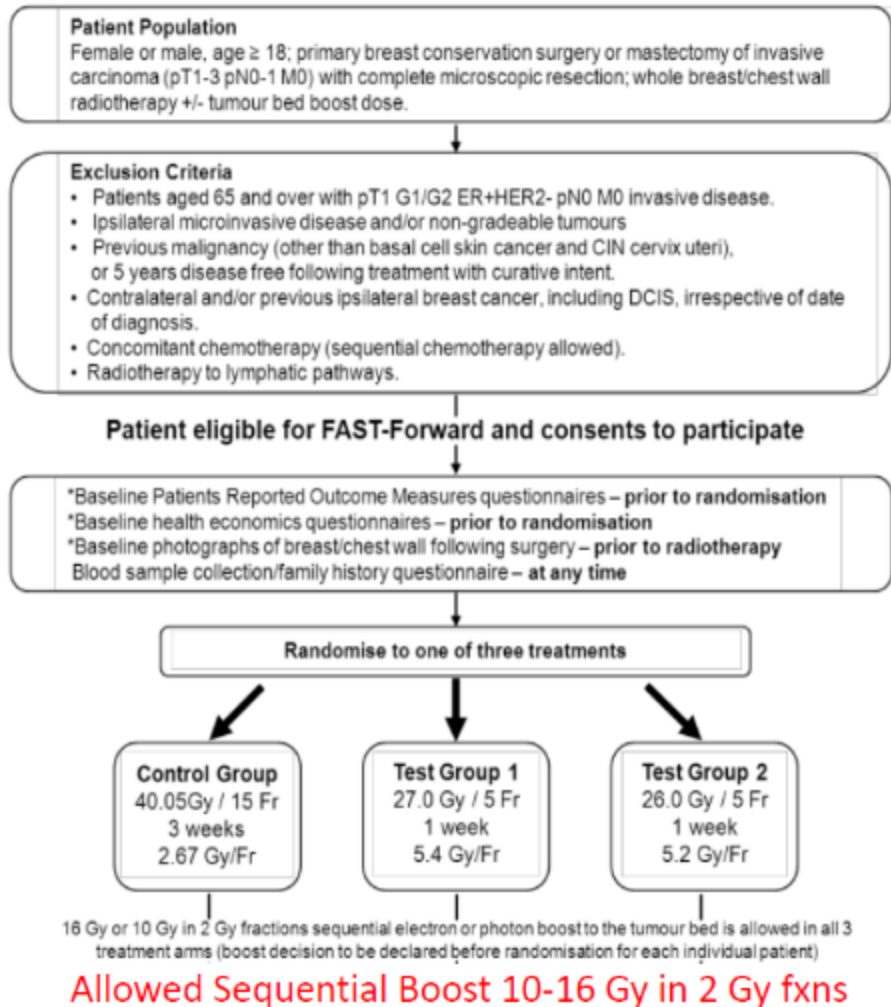
AEs were graded with NCI CTCAE version 4.



Fast-Forward RT – Brunt et al

FAST-Forward hypofractionation:

→ is 26 Gy / 5 fx WBI = 40 Gy / 15 fx WBI



2215 patients following breast conserving surgery randomized to **40Gy in 15** fractions versus **27Gy in 5** fractions versus **26Gy in 5** fractions

FAST-Forward Toxicities:

Acute skin toxicities reported. Acute toxicity substudy 1 – Worst acute CTCAE score according to treatment.

Worst RTOG grade (on or post RT)	40 Gy/15F N = 44 N (%) ^a	27 Gy/5F N = 51 N (%) ^a	26 Gy/5F N = 52 N (%) ^a
0	0	2 (4)	3 (6)
1	14 (32)	24 (47)	32 (62)
2	24 (55)	20 (39)	14 (27)
3	6 (14)	5 (10)	3 (6)
4	0	0	0
Percentage of RTOG grade 3+ (upper limit of one-sided 95% CI)	13.6 (25.2)%	9.8 (19.5)%	5.8 (14.2)%

^a Percentages calculated from those evaluable.

	40 Gy	27 Gy	26 Gy
Any adverse event in breast/chest wall	10.6%	15.9%	12.2%
Breast distortion	4%	6.1%	5%
Breast shrinkage	5.8%	8.5%	6.2%
Breast induration (outside tumor bed)	0.8%	2.3%	1.6%
Telangiectasia	1%	1.6%	1.6%
Breast or chest wall edema	1.5%	3.4%	2.4%
Breast or chest wall discomfort	3.8%	4.3%	4%

- More late toxicities in 27 Gy arm than 40 Gy arm
- 26 Gy arm at least comparable if not better than 40 Gy arm but potential increased induration in 26 Gy arm developing long-term

WBI vs PBI: Trials for Partial Breast Irradiation

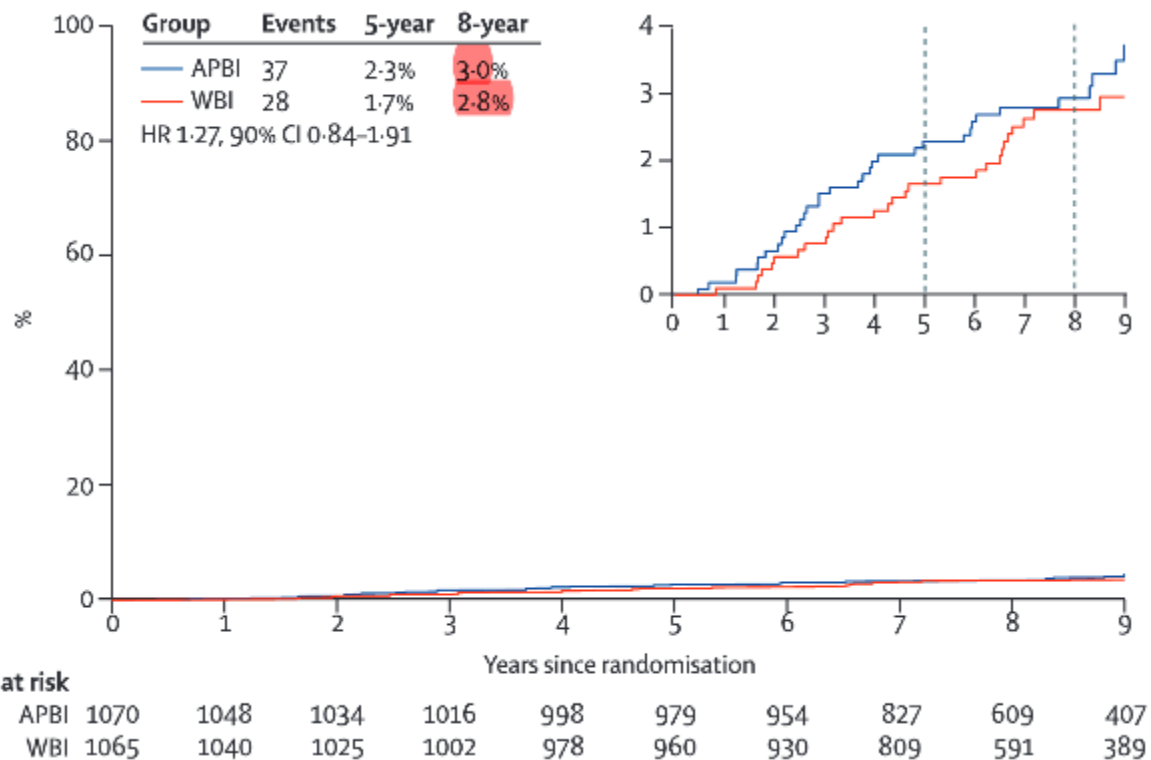
Enrollment

1. Majority of patients age ≥ 50 years
2. Tumor size < 2 or 3 cm
3. Node negative
4. Surgical margins > 2 mm
5. Grade 1 or 2
6. ER+, Her2-
7. Excluded EIC, Invasive lobular carcinoma, LVSI

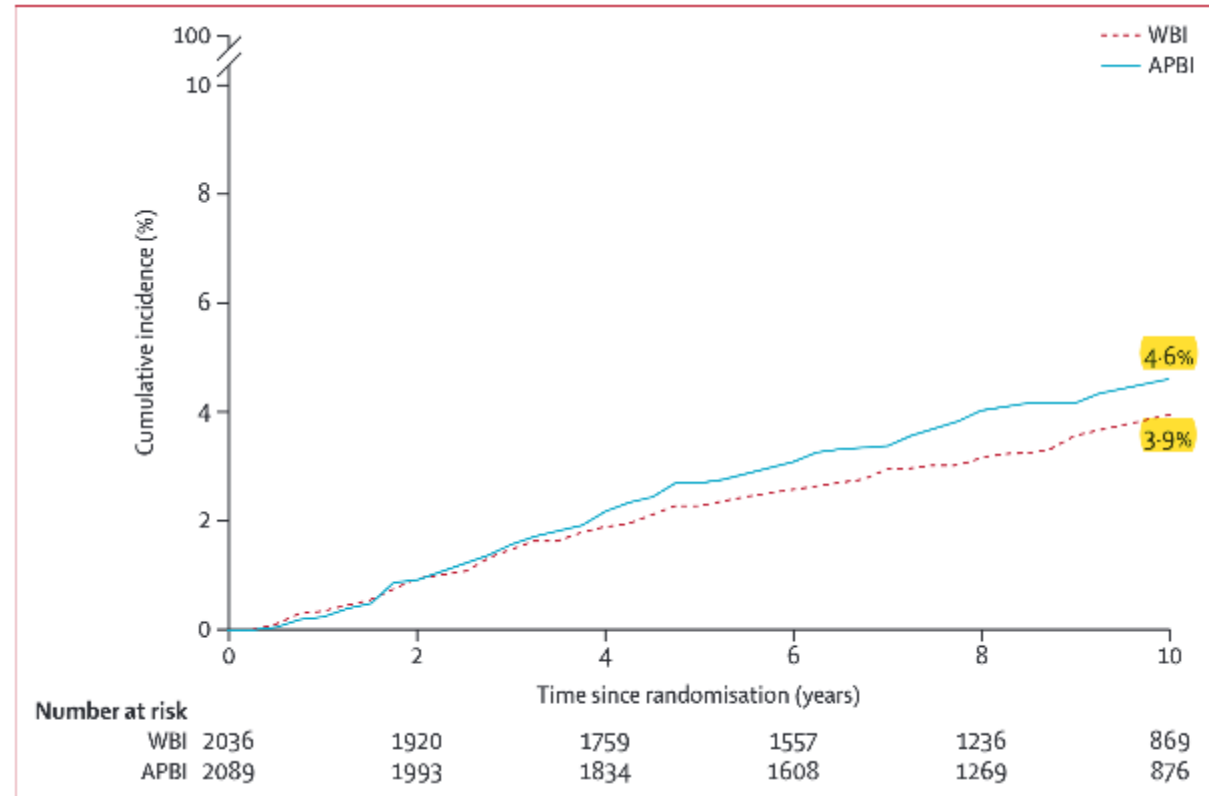
PBI



ACCELERATED partial breast irradiation? RAPID and NSABP B-39 (38.5Gy in 10fx BID; 1 week)

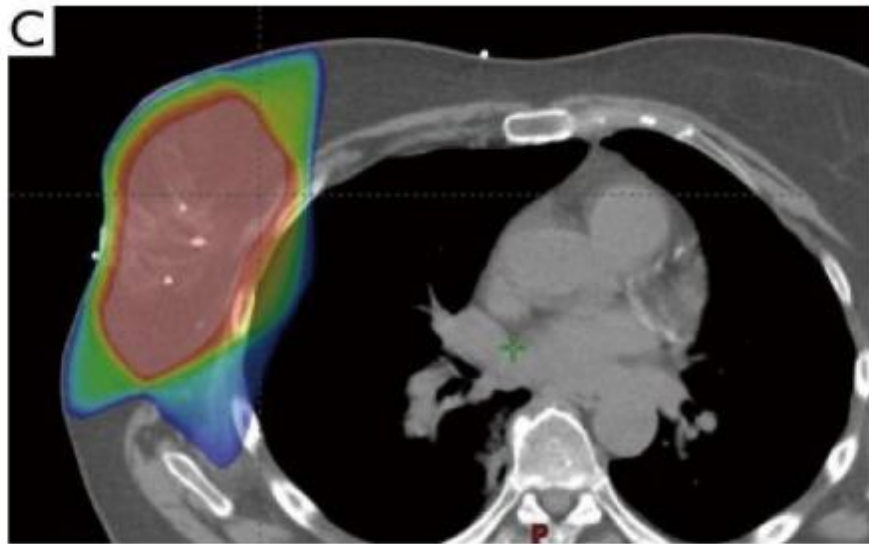


RAPID Whelan et al. Lancet 2019

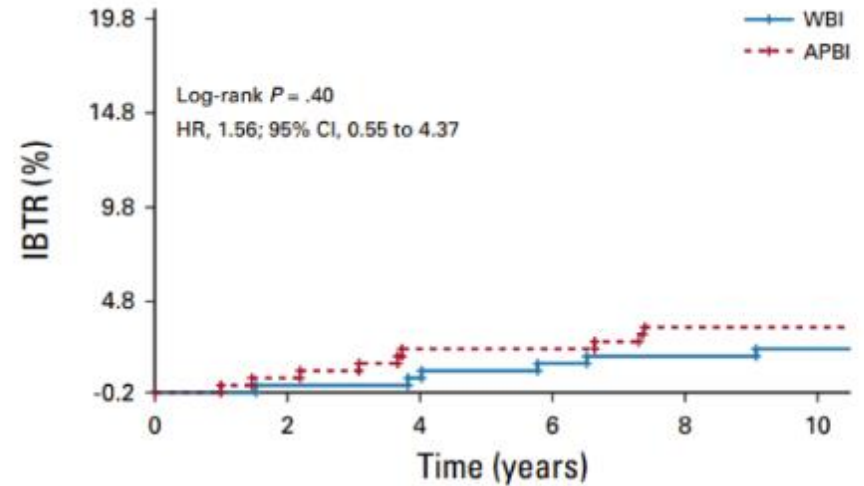


NSABP B-39; Vicini et al. Lancet 2019

Florence Trial for 5 fraction APBI at 10 years

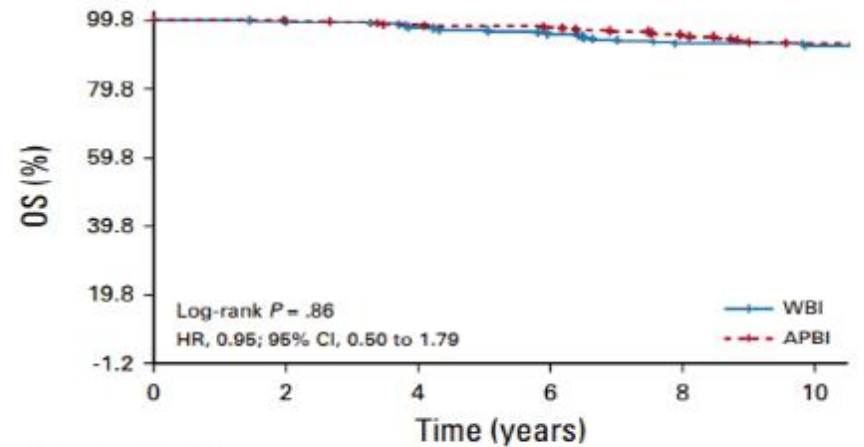


IMRT APBI 30 Gy in 5 fxns QOD



No. at risk (No. of events):

	0	2	4	6	8	10
APBI	260 (0)	257 (2)	251 (6)	249 (7)	189 (9)	141 (9)
WBI	260 (0)	257 (1)	253 (2)	246 (4)	220 (5)	168 (6)



No. at risk (No. of events):

	0	2	4	6	8	10
APBI	260 (0)	259 (1)	256 (4)	254 (6)	196 (12)	144 (18)
WBI	260 (0)	258 (1)	254 (6)	249 (11)	223 (18)	172 (20)

Switching Gears.... INCREASING the Volume ??

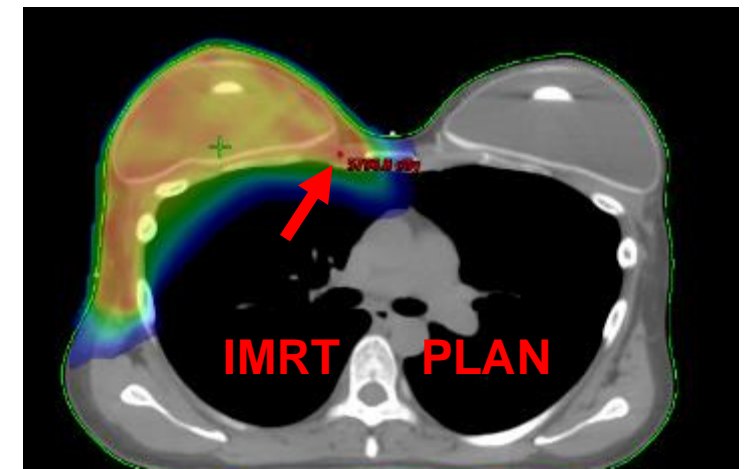
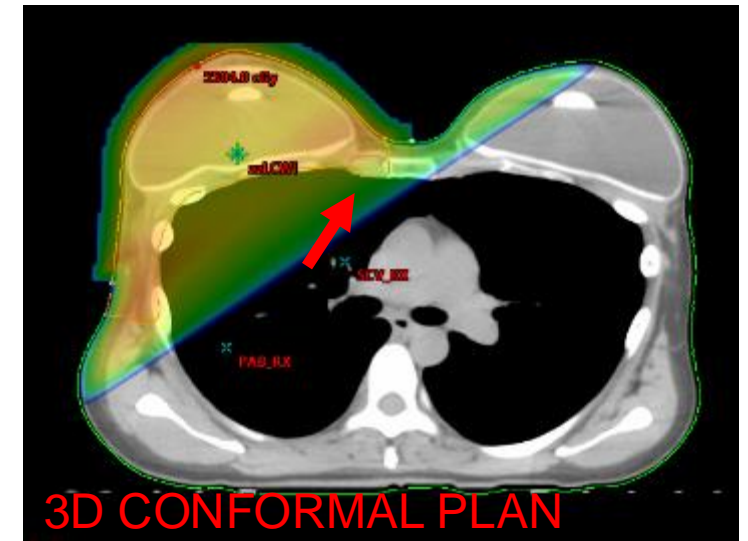
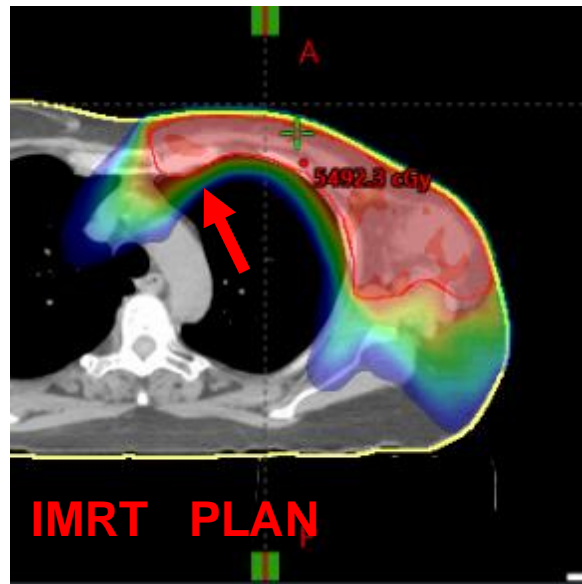
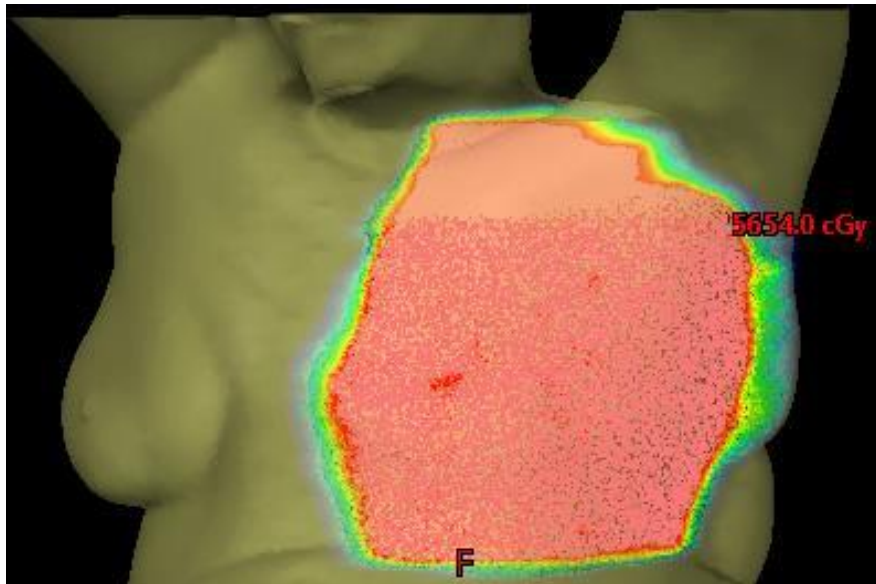


Regional Nodal Irradiation

Treatment directed to:

Lumpectomy cavity/Chest wall AND

Regional Nodal Basins (axilla, supraclavicular & internal mammary nodes)



RNI / PMRT for N1 disease

- Risk factors to consider
 - LVI (focal vs extensive)
 - ENE (< 2mm vs >2mm)
 - Young age (40-50 yo)
 - Premenopausal
 - Number of involved nodes
 - Ratio of involved nodes
 - Total number of nodes sampled
 - ER negative
 - Medial location
 - Poorly differentiated
 - Triple negative
 - Large primary (>2 cm, >4 cm)
 - Close/positive margins
 - Multicentric disease
 - Microscopic involvement of skin, nipple, skeletal muscle, pec fascia
 - Oncotype DX score

RNI: including IMN coverage for earlier stage patients

Locoregional recurrences <10% in both arms of MA20 and EORTC 22922...

However:

- Nodal recurrences have poor prognosis (25-50% OS)
- We do not image patients to detect nodal recurrences
- Nodal recurrences probably under-estimated
- The patients in EORTC and MA 20 were low risk

→ 3 large studies show decreased mets +- improved breast cancer survival for treating nodes and IMN chain

- Danish – IMN only
- MA20 – Axilla+SCV+IMN
- EORTC 22922 – SCV+IMN

Is treating the IMNs necessary? DBCG-IMN.

Basics

- Nationwide prospective cohort study (2003-2007)
- N+ (excluding micromets)
- All received ALND
- Mastectomy or lumpectomy
- Treated with
 - **Left breast: Whole-breast/CW/axilla/SCV w/o IMNs**

VS

- **Right breast: Whole breast/CW/axilla/SCV w IMNs**

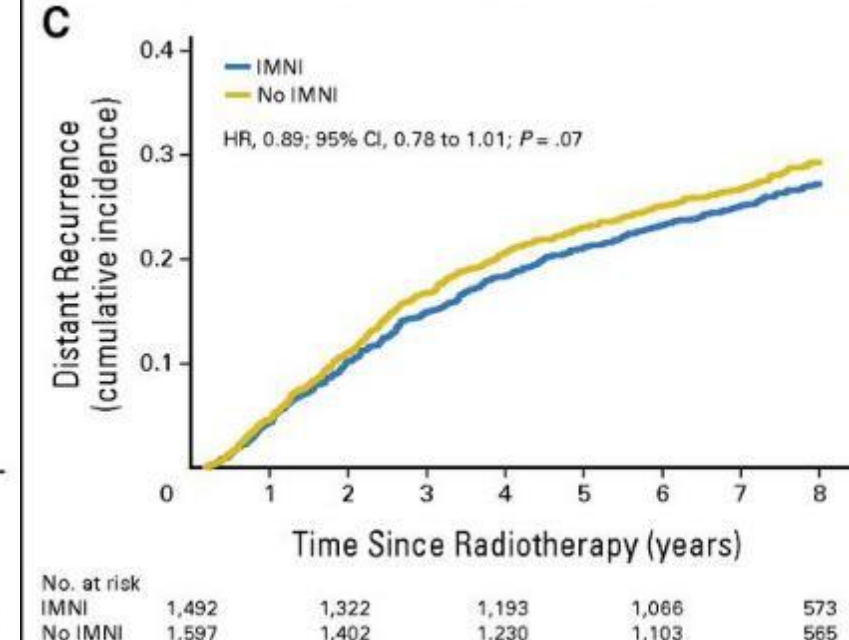
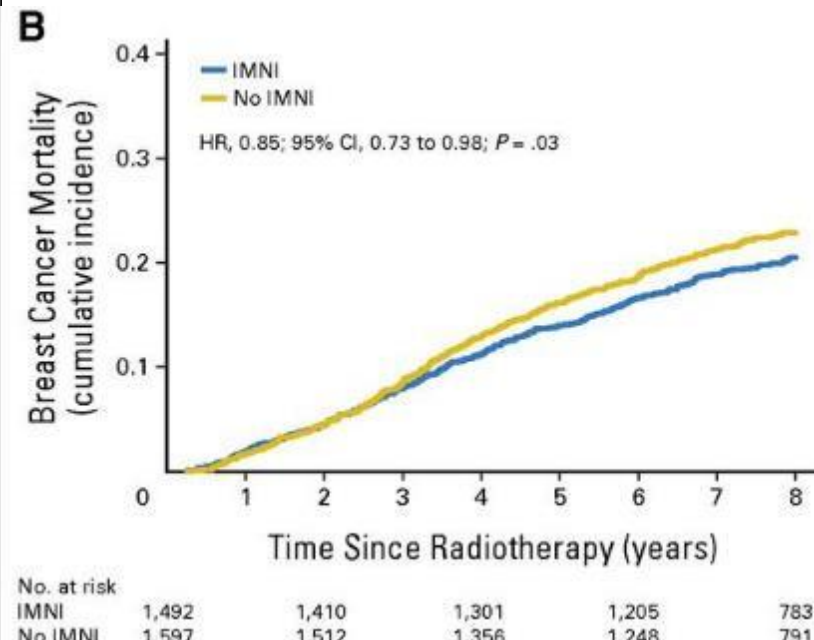
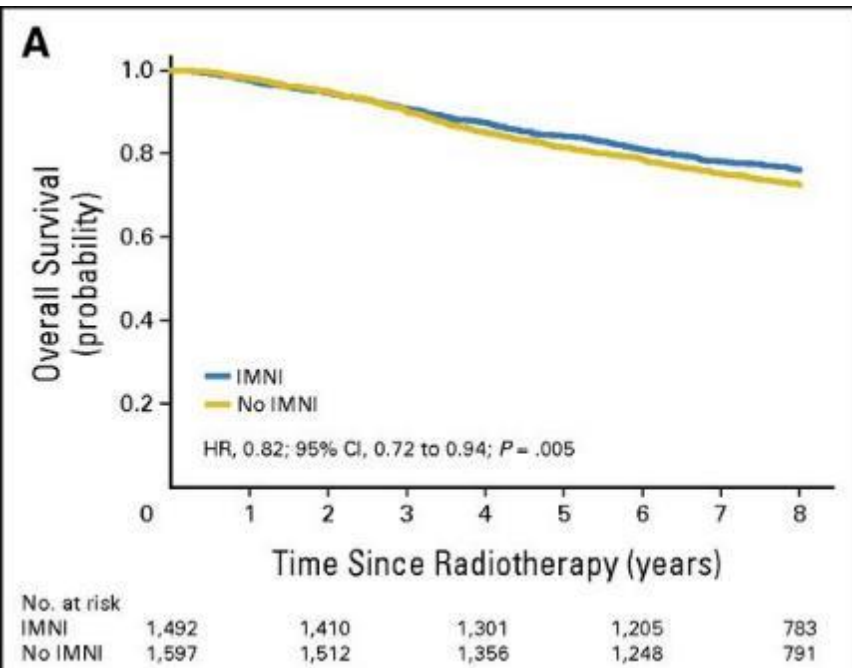
Table 1. Demographic and Clinical Characteristics

Characteristic	Breast Cancer Laterality			
	Right Side (n = 1,492)		Left Side (n = 1,597)	
	No.	%	No.	%
IMNI				
Yes	1,437	97	161	10
No	49	3	1,432	90
Unknown	6	< 1	4	< 1
Other radiotherapy				
Axillary level I treated	273	18	296	18
Boost to lumpectomy cavity	192	13	192	12
Type of surgery				
Mastectomy and axillary clearance	962	65	1,054	66
Breast conservation and axillary clearance	530	35	543	34
Type of systemic therapy				
Endocrine therapy	702	47	745	47
Chemotherapy	278	18	310	19
Both	514	35	542	34
Age at surgery, years				
< 35	37	2	40	2
35-49	421	28	433	27
50-59	534	36	578	36
≥ 60	500	34	546	34
Median (range)	56 (22-70)		56 (27-70)	
Menopausal status				
Premenopausal	612	41	649	41
Postmenopausal	880	59	948	59
Tumor size, mm				
0-20	625	42	653	41
21-50	773	52	836	52
> 50	92	6	106	7
Unknown	2	< 1	1	< 1
Tumor location*				
Medial or central	582	39	644	40
Lateral	907	61	950	59
Unknown	3	< 1	3	< 1
No. of positive lymph nodes				

Is treating the IMNs necessary? DBCG-IMN.

Results

- 3089 patients – **IMN** vs **noIMN**
- **8-year follow-up**
 - **OS** difference (**75.9% vs 72.2%; p=0.005**)
 - BCSM benefit (**20.9% vs 23.4%; p=0.03**)
 - Distance recurrence benefit (**27.4% vs 29.7%; p=0.07**)
 - DMFS benefit (**78.0% vs 75.0%**)



MA.20: RNI primarily confers a DFS benefit.

- N+ or high risk node negative (>5cm; or >2cm w high risk features)
- N+ all got ALND
- All breast conserving surgery (no mastectomies)
- Randomized to
 - **Whole-breast** versus
 - **Whole breast + axilla + SCV + IMNs**

	WBI	WBI + RNI
Isolated LRR	6.8%	4.3%
LR	4.1%	3.6%
RR	2.5%	0.5%
DFS 10- years	77%	82%

EORTC 22922 – RNI improves distant recurrence and DFS.

- N+ or High risk node negative (medial/central tumors)
- Almost all with ALND
- Mastectomy or lumpectomy
- Randomized to
 - **Whole-breast/CW** versus
 - **Whole breast/CW + axilla + SCV + IMNs**

	WBI/CW	WBI/CW + RNI
LR	5.3%	5.6%
RR	4.2%	2.7%
Distant recurrence	19.6%	15.9%
DDFS 10-years	75%	78%
DFS 10-years	69%	72%

Risk factors in consideration of RNI for 0-3+ nodes.

	Primary Risk Factors	Secondary Risk Factors
Risk factors	Age < 40 TNBC Extensive LVI/Soft tissue emboli	Grade 3 (if ER positive) Medial quadrant >3.0 cm High O-DX Age 40-50 LVI, NOS ECE>2mm

Overall risk threshold for RNI to be determined by **multidisciplinary** consensus, and **jointly between patient and physician**.

Current MSKCC approach.

Risk Matrix of Primary and Secondary Risk Factors for RNI in patients undergoing BCT and for PMRT in patients undergoing mastectomy *with* ALND^{1,2}

	Primary Risk Factors	Secondary Risk Factors
Risk factors	Age < 40 TNBC Extensive LVI/Soft tissue emboli	Grade 3 (if ER positive) Medial quadrant >3.0 cm High O-DX Age 40-50 LVI, NOS ECE>2mm
Regional nodal irradiation/PMRT is indicated if the following conditions exist:		
Node-negative⁴	All 3 plus 1 secondary	2 primaries+ 3 secondaries
Micromets⁴	Extensive LVI	2 primaries+2 secondaries OR 1 primary + 3 secondaries
1+ node	Extensive LVI OR (combination of TNBC, ≤40) ³	LVI with 1 secondary OR 3 secondaries
2+ nodes	Any primary	LVI OR age 40-50 OR 2 secondaries
3+ nodes	RNI for all	RNI for all

- Micromets typically do not require an AXLND or PMRT
- Macromets on SLNB typically requires AXLND unless planned to get PMRT
- AMAROS used to obviate the need for both AXLND and PMRT in patients with 1-2 + SLNs and risk factors for PMRT

Dose Escalation Talk Overview

Common Topics in Escalation

- RT for Breast Cancer
- NCCN
- RT DOSE: Lumpectomy Cavity Boost Dose and SIB
- Faster RT – UK Fastforward & Florence PBI Trials
- RT Volume for N1 Disease

Future/Challenging Topics

- Re-RT Considerations
- RT for Gross Residual or Recurrent Disease
- Radiation Guided Nanoparticles



Management of IBR with BCS + reRT

RTOG 1014

- Phase II, prospective clinical trial
- June 2010- June 2013

Eligibility Criteria

IBTR

- <3cm
- 0-3+ LN
- Unifocal
- >1 year after BCT with WBI

BCS with negative margins



CT confirmed target
lumpectomy cavity

Adjuvant PBrI

- 3-D conformal technique
- 1.5 Gy BID
- Total dose 45 Gy in 30 fractions

Endpoints

- Second in-breast recurrence, DMFS, OS, mastectomy rate, AE >1 yr after treatment

Management of IBR with BCS + reRT

58 patients

-Mean age 65 yo

-Median follow up 5.5 yrs

-Median time to recurrence 13.4 yrs (1.6-29.7 yrs)

Prior WBI

-Median dose 50.4 Gy (45-61.2)

-Median fraction size 1.8 Gy (1.5-2.2)

-41 (80%) patients received boost

IBTR Characteristics

-22 (38%) Stage 0

-35 (60%) Stage 1

-1 (2%) Stage IIA

Characteristic		Finding
Race/Ethnicity	Asian	1 (12%)
	Black/African American	8 (14%)
	White	48 (83%)
Histologic Subtype	DCIS	23 (40%)
	Invasive	35 (60%)
Largest dimension, cm	<1	13 (57%)
	1-2	6 (26%)
	>2	4 (17%)
Histologic grade	Low	9 (16%)
	Intermediate	31 (54%)
	High	18 (31%)
ER Status	Positive	44 (76%)
	Negative	14 (24%)
PR Status	Positive	33 (57%)
	Negative	25 (43%)
Her2 Status	Positive	10 (17%)
	Negative	37 (64%)
Axillary surgery	Yes	24%
	No	64%
Systemic therapy	Chemotherapy	4 (7%)
	Endocrine therapy	22 (38%)
	Both	2 (3%)
	None	30 (52%)

Re-RT BCS & Toxicity on 1014

Treatment related AEs acceptable

- Grade 1 : 14 (25%)
- Grade 2: 15 (26%)
- Grade 3: 4 (7%)
- **No grade 4 or 5 adverse events**

Table 4.

Distribution of Patients by Highest-Grade Adverse Event by Specific Adverse Event Term Occurring More Than 1 Year From Completion of Partial Breast Reirradiation^a

System Organ Class or Term	Adverse Event Grade, No.				
	1	2	3	4	5
Infections and infestations					
Total	0	1	1	0	0
Breast infection	0	0	1	0	0
Musculoskeletal and connective tissue disorders					
Total	17	5	1	0	0
Fibrosis deep connective tissue	9	3	1	0	0
Reproductive system and breast disorders					
Total	9	6	3	0	0
Breast atrophy	4	5	1	0	0
Breast pain	9	1	1	0	0
Other ^b	2	0	1	0	0
Skin and subcutaneous tissue disorders					
Total	12	9	1	0	0
Skin induration	4	4	1	0	0
Overall highest grade, No. (%)	14 (24.6)	15 (26.3)	4 (7.0)	0	0

Re-RT BCS & Local Control

Characteristics of patients with an in-breast recurrence

Location	Histologic Subtype	Grade	Stage	Tumor Size , cm	ER +	PR +	HER2 +	Dissection/ Biopsy	Time from registration to failure, y
Outside treatment field	DCIS	Intermediate	0	1.3	No	No	ND	No SLNB/No ALND	2.6
Within treatment field	DCIS	Intermediate	0	1.5	Yes	Yes	No	No SLNB/No ALND	2.9
Within treatment field	DCIS	High	0	1.0	Yes	Yes	No	SLN not identified /No ALND	4.1
Outside treatment field	DCIS	Intermediate	0	0.2	Yes	Yes	No	No SLNB/No ALND	5.1

- Average time to recurrence : 3.7 yrs
- 3-yr cumulative incidence IBR 3.4% (95% CI, 0.6%-10.7%)
- Significant reduction in LRR with addition of PBrl in comparison to BCS alone (25% vs 3.4%; $p < 0.01$)

Re-RT PBI : Alternative Fractionation

- Utility of hypo-fractionated and ultrahypo-fractionated PBI for re-irradiation
 - Retrospective analysis, 2-institutions;
 - 2015-2021
 - median f/u 16mo
- 66 pts
 - 57% hyperfractionation BID
 - 27% conventional fractionation QD
 - 6% QOD hypofractionation
 - 4.5% QOD ultrahypofractionated
- Are there equally effective alternative regimens that are more convenient ?

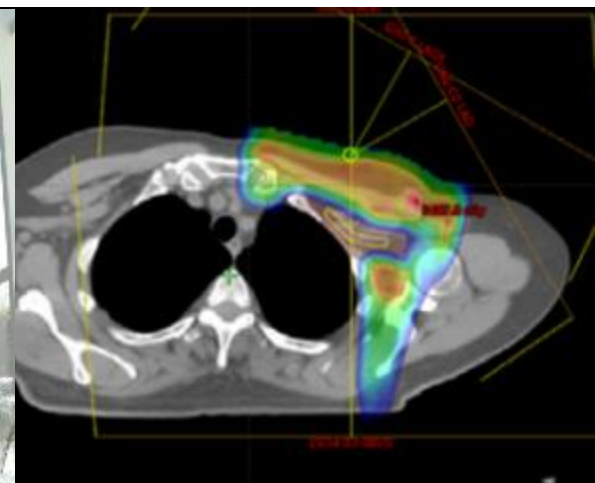
Toxicity	Acute ≤ 3 months n = 66			Late > 3 months n = 61		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Fatigue	10 (15)	6 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatitis	60 (91)	6 (9)	1 (1.5)	0 (0)	0 (0)	0 (0)
Breast pain	12 (18)	1 (1.5)	0 (0)	4 (6.5)	2 (3)	0 (0)
Fibrosis	7 (11)	3(4.5)	0 (0)	11 (18)	6 (10)	1 (1.5%)
Seroma	7 (11)	2 (3)	0 (0)	2 (3)	0 (0)	0 (0)
Breast atrophy	3 (4)	2(3)	0 (0)	5 (8)	5 (8)	0 (0)
Lymphedema	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)
Telangiectasia	0 (0)	0 (0)	0 (0)	1 (1.5)	1 (1.5)	1 (1.5%)

Re-RT → Patient Selection and Treatment Approach



RTOG 1014

New York Proton Center (225 E 126th St, NY, NY)



Plexus Tunneling with PBS-Proton
J. Choi et al, ADRO 2023

- Opened in 2019
- 1st and only proton center in the state of New York
- Partnership with MSKCC, Mt. Sinai Health System, and Montefiore Medical Center
- 5 in-house physicians
- 20 partner physicians



J. Isabelle Choi, MD, FACRO

Clinical Director, Director of Research

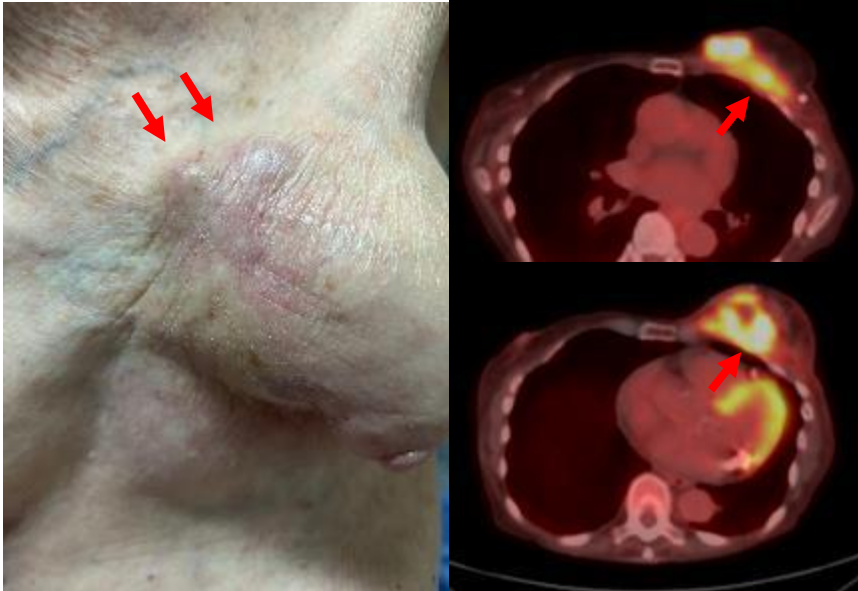
MSK Breast Proton Therapy Lead

choij3@mskcc.org

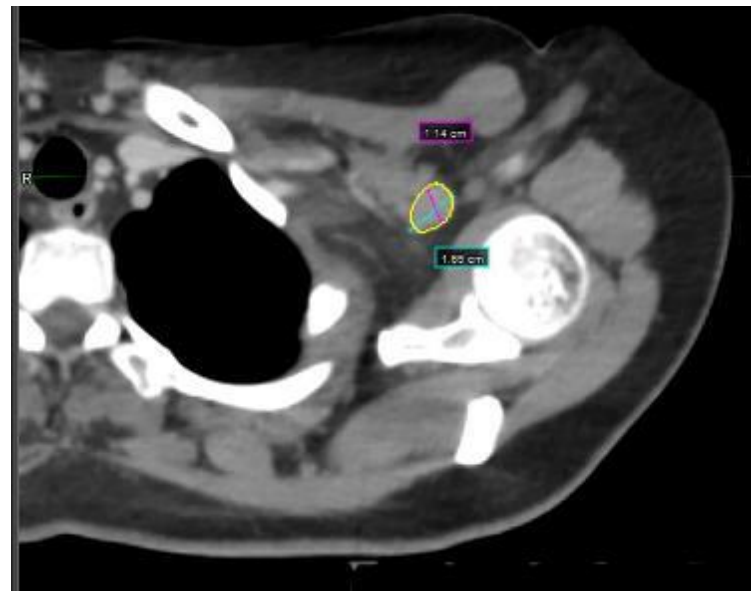
(617) 833-5225

Radiation Approach for Progressive/Unresectable or Residual / Recurrent disease

POD & Unresectable on NET & CDK4/6(-)



Residual/POD Nodes post NAC/Mtx



Recurrent skin mets



Advanced Radiation Techniques

- Dose Painting IMRT (50 →54→58→60 Gy)
- Organ Sparing IMRT
- Expedited RT Planning
- Adaptive re-planning

Consideration of concurrent chemo?

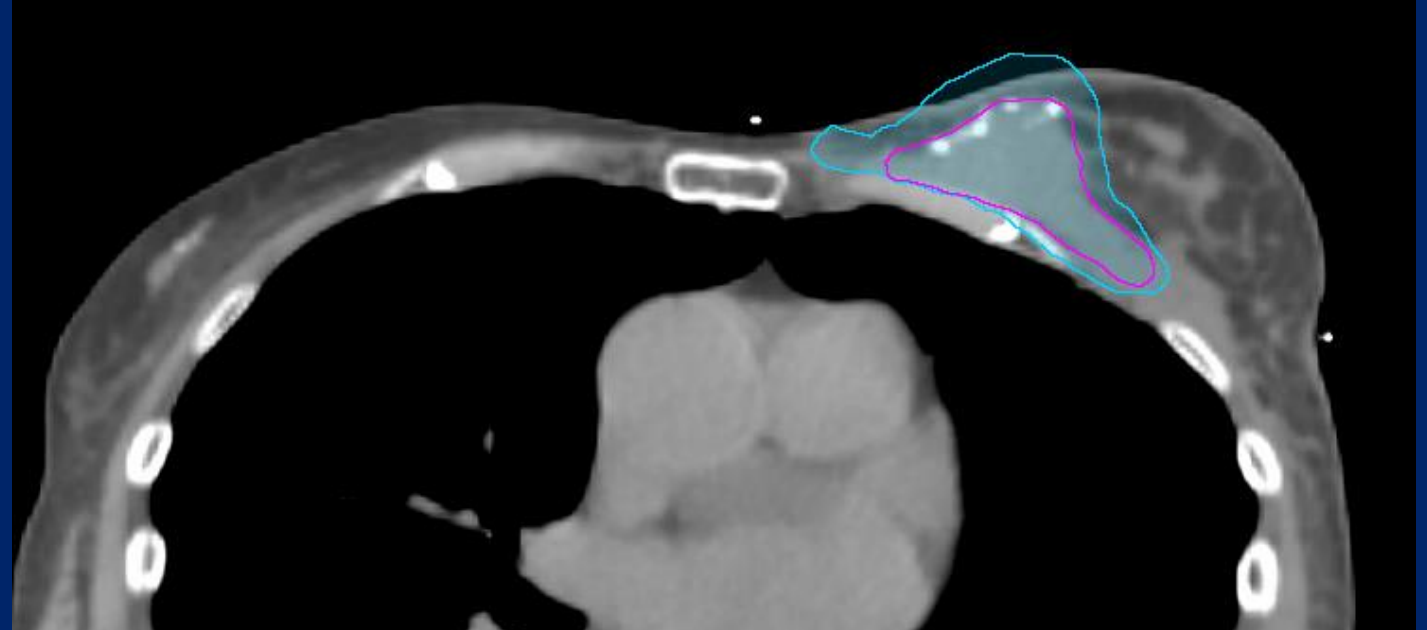
Concurrent Chemo	Breast Ca Study	Other Cancer experience
Cisplatin	MSK #15-032 Phase II for MBC	Standard for H&N SqCC (70Gy)
Capecitabine	Phase II, MDACC; for IBC	Standard for Rectal Ca (55Gy)
PARP-i	MSK #18-002, Phase I, non-pCR post NAC	Phase II Prostate, Pancreas, Lung

Expedited Adaptive re-planning VMAT

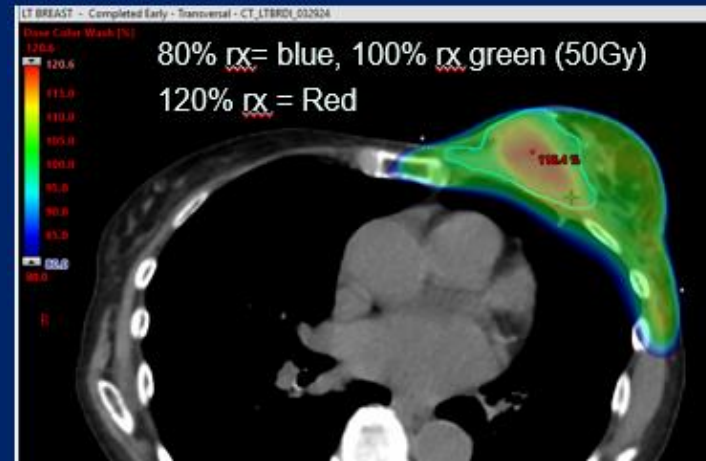
- Initial tumor blue (105cc)
IntraTx tumor pink (65cc)
(resim @ fx 15 of 25)

Plan: 50/54/60gy / 25fx
(60Gy only center of tumor)

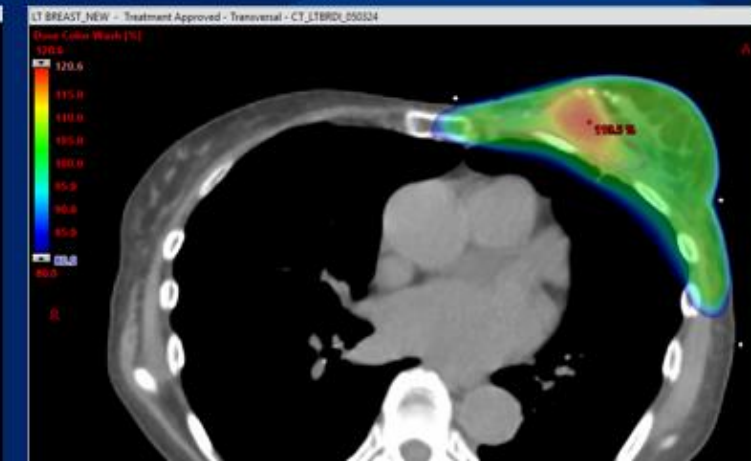
Concurrent Capecitabine



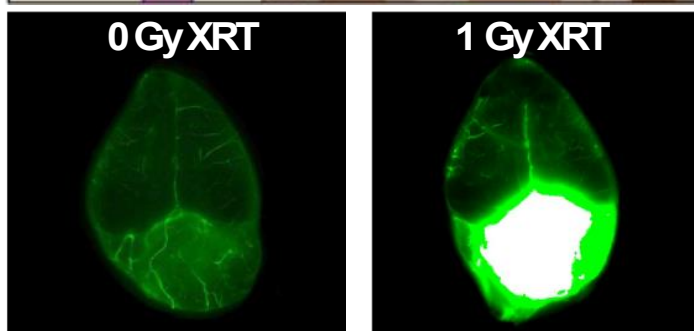
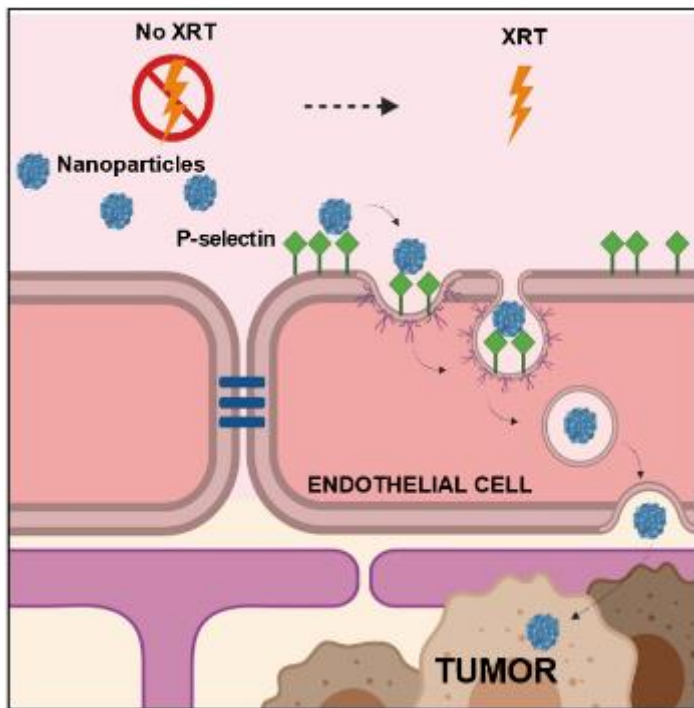
Initial sim plan



Re-plan (gtv off cw/skin)

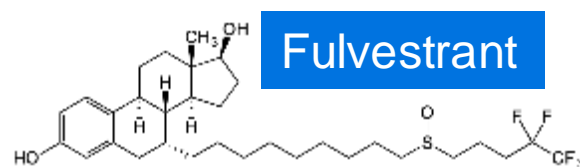
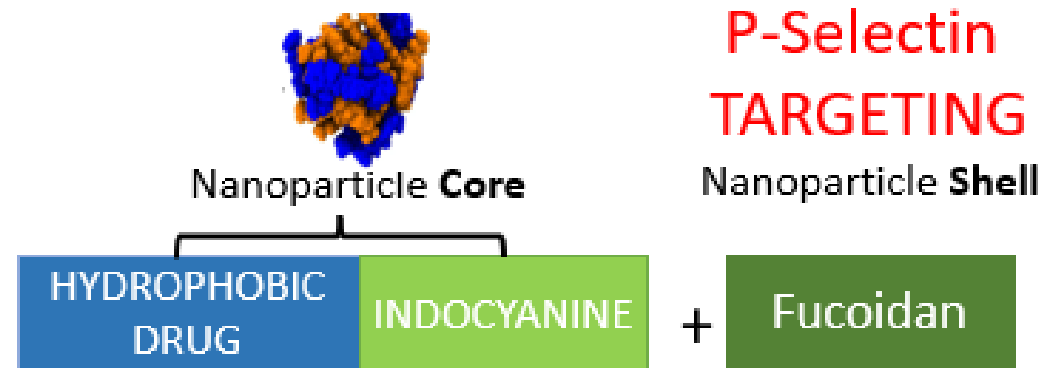


Radiation Guided Nanoparticles: ICG based, P-Selectin targeting NERDs



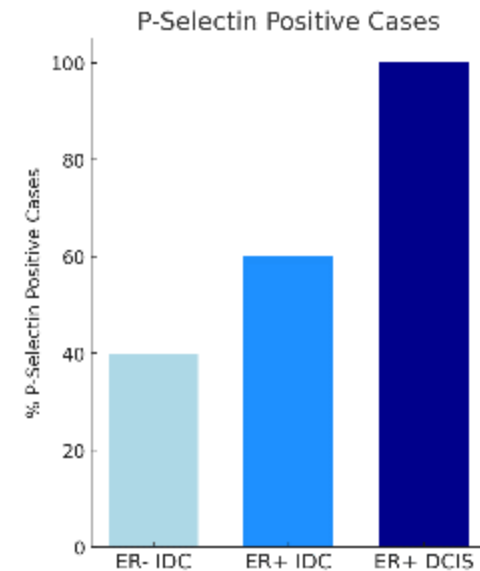
ICG Fucoïdan Nanoparticle

Ex: Medulloblastoma Mouse brain

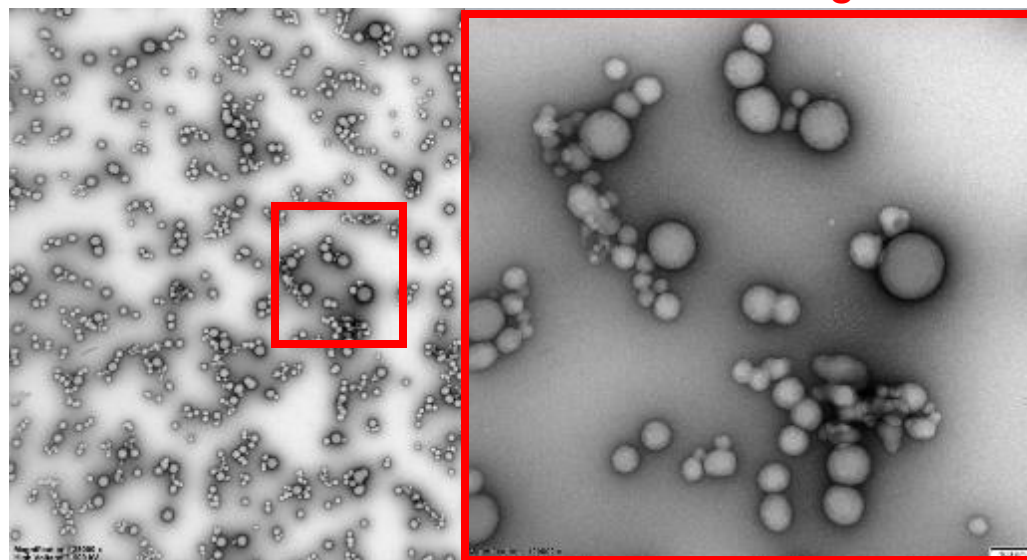


NERDs:

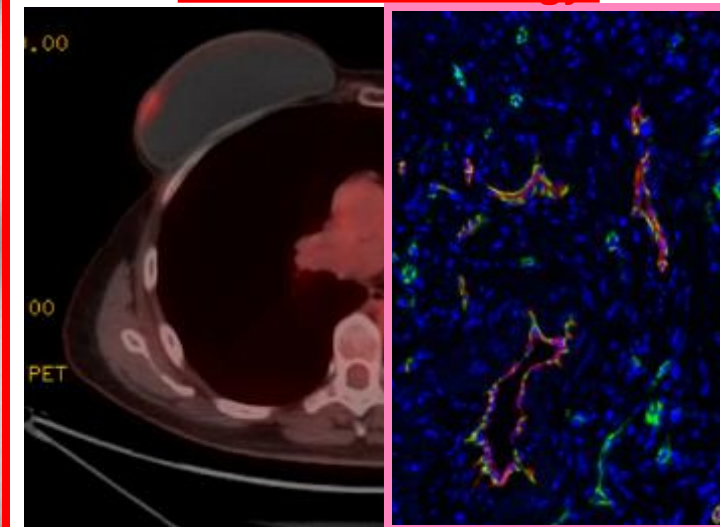
Nano ER Degraders



P-Selectin histology:



Electron Microscopy of NERDs



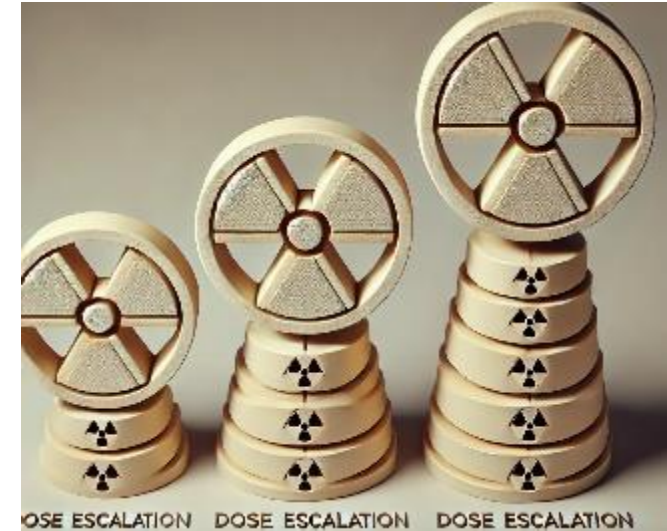
Recurrent ER+ IDC

Dose Escalation Summary



Common Topics in Escalation

- RT for Breast Cancer
- NCCN : **Observation, WBI, PBI, RNI**
- RT DOSE: **40 Gy / 15 fx with SIB to 48Gy**
- Faster RT – **5fx RT ! WBI and PBI**
- RNI/PMRT for N1 Disease in **well-selected pts**



Future/Challenging Topics

- Re-RT with BCT option!
- RT for Gross Residual or Recurrent Disease
- Look out for NERDs !!



Radiation Dose Escalation for Breast Cancer

2024 Breast Cancer Symposium

Thank You!!

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Memorial Sloan Kettering
Cancer Center



RADIATION DOSE ESCALATION
FOR BREAST CANCER