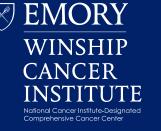


# Where Science Becomes Hope

IS PMRT NEEDED IN PATIENTS WITH NODAL PCR FOLLOWING NEOADJUVANT CHEMOTHERAPY?

# PRO

Reshma Jagsi, MD, DPhil Lawrence W. Davis Professor and Chair Department of Radiation Oncology Emory University School of Medicine Winship Cancer Institute



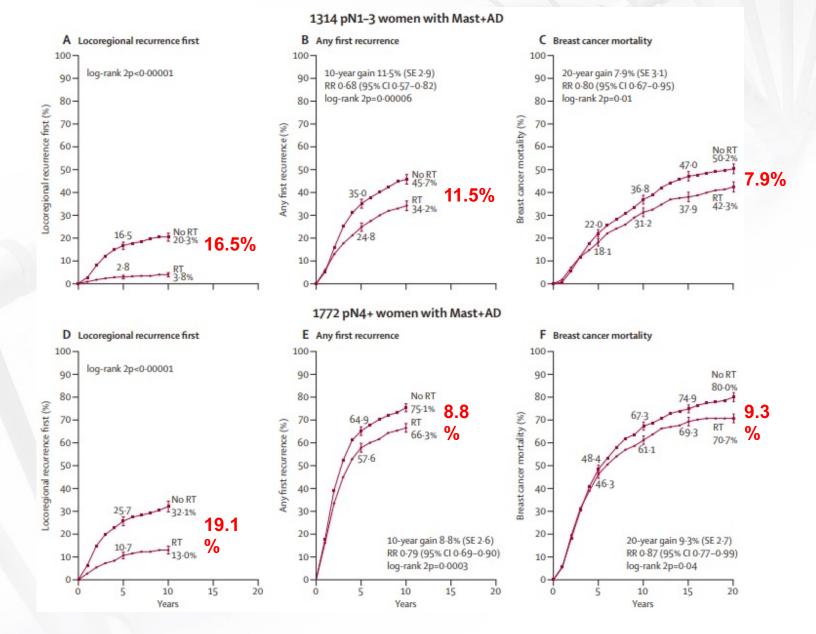


**Cancer Center** 

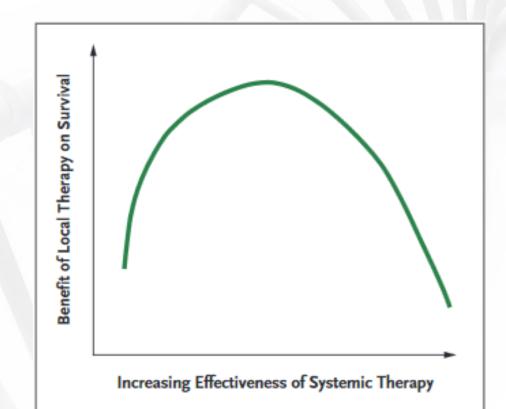
## **BENEFIT OF PMRT**

Landmark trials

EBCTCG, Lancet 2014; 383:2127-35



# HYPOTHETICAL BENEFIT OF LOCAL TUMOR CONTROL ON SURVIVAL WITH INCREASING EFFECTIVENESS OF SYSTEMIC THERAPY



Punglia RS et al. N Engl J Med. 2007;356(23):2399-2405.

## **2023 EBCTCG META-ANALYSIS**

17 "randomized trials" starting before 2009 had been conducted worldwide in which the only difference between the 2 treatment groups involved irradiation of regional lymph nodes in 1 or more of 3 sites: the IMC, SC fossa, and axilla

- 1 not RCT: DBCG study where laterality used to determine RNI to the IMN (only administered for right-sided disease)
- Surgery, any RT to chest wall or breast, & systemic therapy same for both study arms (unconfounded comparisons)
- EBCTCG was able to collect individual pt data from all but one (165 patients)
- 8 older trials where RT technique was direct anterior photon beams alone
  - Usually these patients did not receive chest wall RT
  - Comparison=RNI vs no RT
  - Only 1.6% of patients received BCS, 20% chemo, 0 endocrine therapy
- 8 newer trials where RT technique was more tailored to spare heart & lung
  - Usually these patients did receive breast or chest wall RT
  - Comparison=more vs less RT
  - 57.7% of patients received BCS, 62% chemo, 61% endocrine therapy

### **FINDINGS**

In the 8 newer trials (12 167 patients), which started 1989-2008:

RNI significantly reduced recurrence (rate ratio 0.88, 95% CI, 0.81-0.95; P=.0008).

The main effect was on distant recurrence as few regional node recurrences were reported.

RNI significantly reduced breast cancer mortality (RR 0.87, 95% CI, 0.80-0.94; P=.0010), with no significant effect on nonbreast-cancer mortality (0.97, 0.84-1.11; P=.63) or on heart disease mortality, contralateral breast cancer incidence, or other second cancer incidence, leading to significantly reduced all-cause mortality (0.90, 0.84-0.96; P=.0022).

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2023;402(10416):1991-2003.

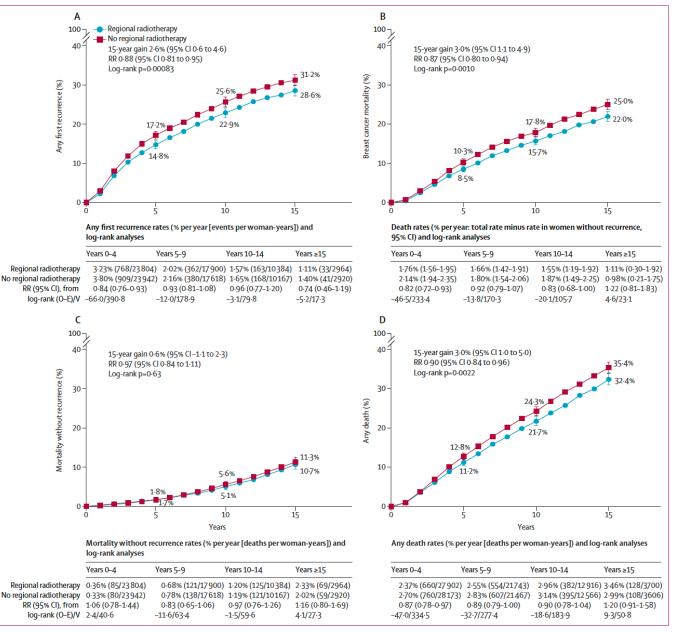


Figure 2: Effect of regional node radiotherapy in the eight newer trials on (A) any recurrence, (B) breast cancer mortality, (C) non-breast-cancer mortality, and (D) any death One newer trial of 1334 women that reported only all-cause mortality is included only in graph D. RR=rate ratio.

## **HETEROGENEITY TESTING**

Proportional reductions in recurrence and breast cancer mortality did not vary significantly according to most treatment or patient or tumor characteristics, including age, nodal status, grade, tumor size, and ER status.

Some evidence to support a previous hypothesis that the proportional effects of RNI were greater for women with medial or central tumors than for women with lateral tumors (P value for heterogeneity of effect for medial or central vs lateral: any recurrence .021; distant recurrence .052; breast cancer mortality .069; overall mortality .40).

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2023;402(10416):1991-2003.

A	Events/women		Regional radiotherapy events			Rate ratio (95% CI)	
	Allocated regional radiotherapy	Allocated no regional radiotherapy	Log-rank O-E	Variance of O-E			
Age at entry (years)							
<40	153/425	155/429	-4-0	70-2		0.94 (0.75-1.19)	
40-49	342/1462	389/1500	-28-8	173-6	-	0.85 (0.73-0.98)	
50-59	437/1874	509/1929	-29-0	225.8	-	0.88 (0.77-1.00)	
60-69	346/1327	391/1365	-17.9	173.4		0.90 (0.78-1.05)	
≥70	48/271	54/251	-6-6	23.8		0.76 (0.51-1.13)	
χ <sub>1</sub> <sup>2</sup> =0·1; p=0·81	40/2/2	541-51	0.0	23.0		0.70(0.31-1.13)	
Nodal status							
pN0	194/1093	228/1095	-18.3	101-9		0.84 (0.69-1.01)	
	603/2812	682/2910	-	-			
pN1-3			-31.6	311-0	-	0.90 (0.81-1.01)	
pN4+	502/1219	553/1232	-32-4	239-5		0.87 (0.77-0.99)	
pN unknown	27/235	35/237	-4-0	14-4		0.76 (0.45-1.27)	
χ <sub>1</sub> <sup>2</sup> =0·0; p=0·85							
Grade							
Low grade	111/672	140/689	-14-2	59-5		0.79 (0.61-1.02)	
Intermediate grade	377/1442	405/1488	-9-1	182-4		0.95 (0.82-1.10)	
High grade	302/1072	371/1130	-30-6	150-4		0.82 (0.70-0.96)	
Unknown grade	536/2173	582/2167	-27-4	265-6	-L-H	0.90 (0.80-1.02)	
χ <sup>2</sup> =0·1; p=0·78						10 B	
Tumour size							
1–20 mm	509/2774	589/2826	-36-3	261-5	-	0.87 (0.77-0.98)	
21-50 mm	713/2286	789/2361	-35.9	349.5		0.90 (0.81-1.00)	
>50 mm	100/274	115/262	-13-1	40-8		0.73 (0.53-0.99)	
Unknown	4/25	5/25	0.1	1-2		1.09 (0.18-6.50)	
	4/25	5/25	1-0	1-2		1.03 (0.10-0.20)	
χ <sub>1</sub> <sup>2</sup> =0·1; p=0·71							
ER status	Name and State of the State	CONTRACT CONTRACT		(1 <b>-</b> (1) - (1)			
ER poor	325/1138	399/1221	-31-8	160-2		0.82 (0.70-0.96)	
ER positive	923/3963	1024/4002	-58-8	464-3		0.88 (0.80-0.96)	
ER unknown	78/258	75/251	0-8	31-2	——————————————————————————————————————	1.03 (0.72–1.46)	
χ <sup>2</sup> =0·6; p=0·43							
Breast quadrant							
Lateral	704/2601	742/2702	-12-1	338-0		0.96 (0.87-1.07)	
Medial or central	567/2409	691/2438	-64-5	293.9	-	0.80 (0.72-0.90)	
Unknown	55/349	65/334	-9.5	25.7		0.69 (0.47-1.02)	
χ <sub>1</sub> <sup>2</sup> =5·3; p=0·021					5		
Breast surgery							
BCS	707/3502	808/3515	-54-2	363-1		0.86 (0.78-0.95)	
Mastectomy	619/1857	690/1958	-29-7	299.9		0.91 (0.81-1.01)	
None, other, or unknown	0/0	0/1			-		
χ <sup>2</sup> =0·4; p=0·52		S.					
Nodes irradiated							
IMC, SCF, and axilla	631/2918	727/2918	-56-6	326-6		0.84 (0.75-0.94)	
IMC, SCF, and axilia			-56-6		-		
	631/1982	704/2104	-	309-7		0.91 (0.82-1.02)	
SCF or axilla	64/459	67/452	-1.2	30-5		0.96 (0.67–1.37)	
χ <sub>2</sub> <sup>2</sup> =1-3; p=0-52							
Use of systemic therapy							
None reported	111/488	109/457	-1-1	50-1		0.98 (0.74-1.29)	
Chemotherapy only	370/1189	412/1236	-18-8	174-5		0.90 (0.77-1.04)	
Endocrine only	403/1539	446/1606	-16-1	199-5		0.92 (0.80-1.06)	
Both	441/2135	531/2165	-53-0	228-5	-	0.79 (0.70-0.90)	
Other or unknown	1/8	0/10					
χ <sup>2</sup> =3·5; p=0·32							
Period of follow-up							
Years 0–1	366/5359	432/5474	-31-4	184-0		0.84 (0.73-0.97)	
Years 2–4	402/4852	477/4897	-34.6	206-8	_	0.85 (0.74-0.97)	
Years 5–9	362/4189		-12-0	178-9	-		
		380/4149				0.94 (0.81-1.08)	
Years ≥10	196/2796	209/2729	-8.3	97-1		0.92 (0.75-1.12)	
χ <sub>1</sub> <sup>2</sup> =1·1; p=0·30							
Overall	1326/5359 (24.7%)	1498/5474 (27-4%)	-86-3	666-8	\$	0.88 (0.81–0.95)	
p=0-00083				0	0.5 1.0 1.5	2.0	
				0	0.5 1.0 1.5	2.0	
					4		

## **ABSOLUTE BENEFITS**

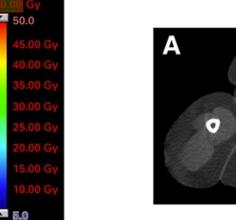
	Regional radiotherapy	No regional radiotherapy	Gain from regional radiotherapy
Any recurre	nce		
pN0	19.0%	21.3%	2.3%
pN1-3	25.6%	28.5%	2.9%
pN4+	46.8%	51.1%	4.3%
Breast cance	er mortality		
pN0	10.9%	12.5%	1.6%
( pN1-3	20.3%	23.0%	2.7%
pN4+	40.5%	45.0%	4.5%

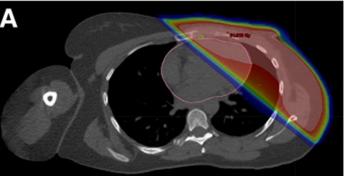
Data are 15-year cumulative risks. The overall rate ratios (RRs) for any recurrence (RR=0.88; figure 3) and breast cancer mortality (0.87; figure 3) were applied to annual rates of any recurrence and breast cancer mortality in the trials, averaged over treatment groups (there was no significant heterogeneity in the proportional reductions [RRs] for any recurrence and breast cancer mortality). pN0=pathologically node negative. pN1–3=one to three involved axillary lymph nodes. pN4+=four or more involved axillary lymph nodes.

*Table 2:* Absolute effect of regional node radiotherapy on 15-year risk of any recurrence and breast cancer mortality by nodal status in 10 833 women in the seven newer trials with data on recurrence

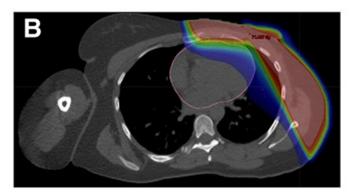
Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2023;402(10416):1991-2003.

#### DECLINING TOXICITY FROM MODERN RT: EXAMPLE OF CARDIAC SPARING

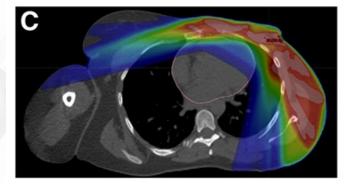




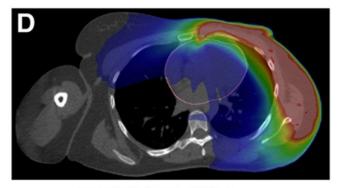
**3DCT Photon Tangents** 



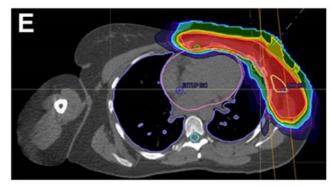
Electron/Photon Matched Fields Plan



**IMRT** Photon Plan



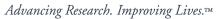
VMAT Photon Plan

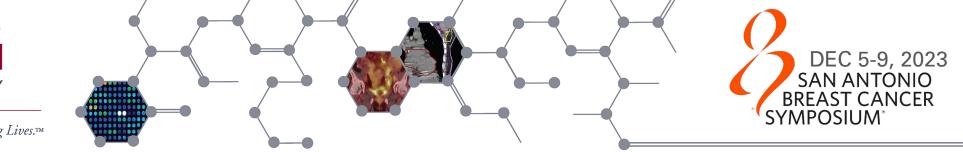


**Proton Plan** 

#### Torres MA et al. J Clin Oncol. 2020;38(20):2299-2309.







# Loco-regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

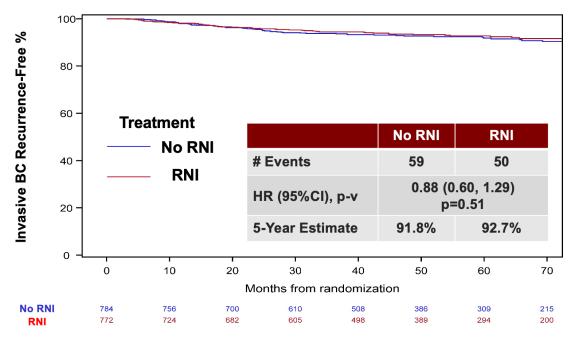
Eleftherios P. Mamounas<sup>1\*</sup>, Hanna Bandos<sup>2</sup>, Julia R. White<sup>3\*</sup>, Thomas B. Julian<sup>4</sup>, Atif J. Khan<sup>5</sup>, Simona F. Shaitelman<sup>6</sup>, Mylin A. Torres<sup>7</sup>, Frank A. Vicini<sup>8</sup>, Patricia A. Ganz<sup>9</sup>, Susan A. McCloskey<sup>10</sup>, Peter C. Lucas<sup>11,12</sup>, Nilendu Gupta<sup>3</sup>, X. Allen Li<sup>13</sup>, Beryl McCormick<sup>5</sup>, Saumil Gandhi<sup>6</sup>, Rahul D. Tendulkar<sup>14</sup>, Vivek S. Kavadi,<sup>15</sup>, Masahiko Okamoto<sup>16</sup>, Samantha Andrews Seaward<sup>17</sup>, William J. Irvin, Jr.<sup>18</sup>, Jolinta Lin<sup>7</sup>, Robert Mutter<sup>19</sup>, Thierry M. Muanza<sup>20</sup>, Andrew A. Muskovitz<sup>21</sup>, Reshma Jagsi<sup>22</sup>, Anna C. Weiss<sup>23,24</sup>, Walter J. Curran, Jr.<sup>7</sup>, and Norman Wolmark<sup>12</sup>

\*These authors contributed equally.

#### LISTEN CAREFULLY & CONTINUE TO REFER PATIENTS FOR DISCUSSION: THIS IS A NUANCED STORY AND IT IS NOT COMPLETE...

```
Median Follow-up Time: 59.5 months (IQR 40.7-74.1) 53% ER+
```

N=1641



#### Invasive Breast Cancer Recurrence-free Interval (IBCRFI)

#### Isolated Loco-Regional Recurrence-free Interval (ILRRFI)\*

