

Impact of Tamoxifen Only after Breast Conservation Surgery for “Good Risk” Duct Carcinoma in Situ: Results from the NRG Oncology/RTOG 9804 and ECOG-ACRIN E5194 Trials

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Disclosures



- Employer: University of North Carolina
- No Disclosures

Background/Rationale

- The impact of radiotherapy (RT) on ipsilateral breast recurrence (IBR) after breast conserving surgery (BCS) for DCIS is the subject of extensive prior and ongoing research.
- NRG/RTOG 9804 showed RT reduced IBR by half at 15 years in a "good risk" population, 15% to 7%.
- RT omission reasonable in this population

NRG/RTOG 9804

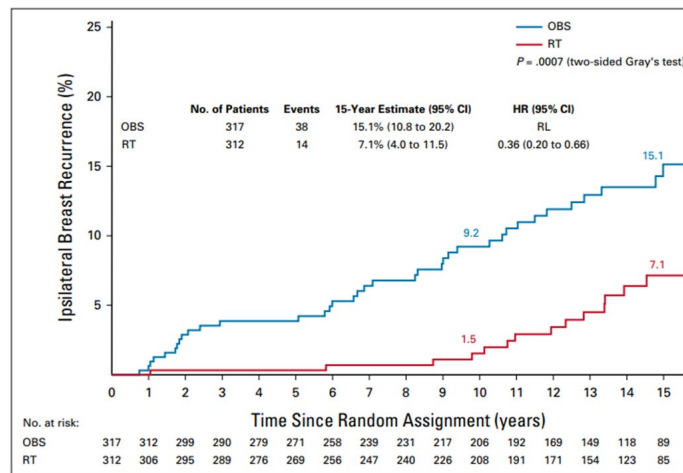


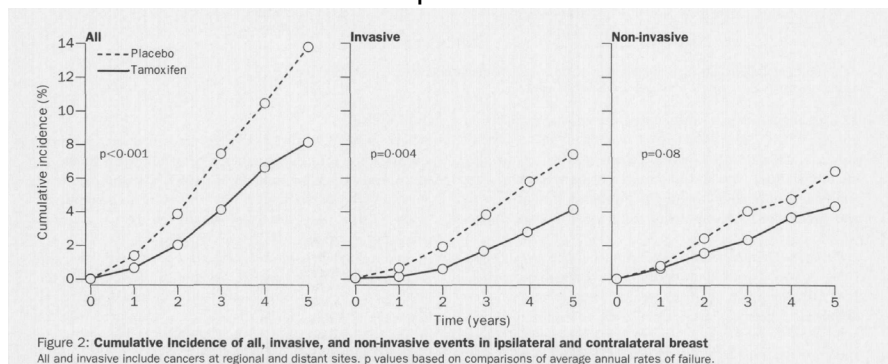
FIG 2. IBR for all randomly assigned patients with follow-up data. HR, hazard ratio; IBR, ipsilateral breast recurrence; OBS, observation; RL, reference level; RT, radiation therapy.

McCormick et JCO 2021

Background/Rationale

- The impact of endocrine therapy is less well established.
 - Historical data shows variable IBR reduction (overall, DCIS, invasive).
 - Most modern studies have left its use at the discretion of the patient and physician.
 - Use is highly variable across practices.

NSABP B-24: all patients received RT



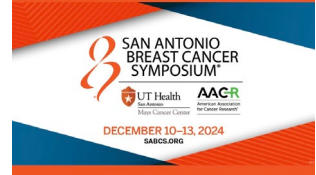
Fisher et al Lancet 1999

UK/ANZ DCIS trial: patients not receiving RT

	Tamoxifen (n/N)	No tamoxifen (n/N)	HR (95% CI)
Patients who did not receive radiotherapy			
Ipsilateral			
Invasive	46/794	51/782	0.89 (0.59-1.33)
DCIS	60/794	84/782	0.71 (0.51-0.99)
All	109/794	140/782	0.77 (0.59-0.98)

Cuzick et al Lancet Oncol 2011

Background/Rationale



- The NRG/RTOG 9804 and ECOG-ACRIN E5194 studies subclassified DCIS into risk groups after BCS based on DCIS size, grade, and margin width.
 - NRG/RTOG 9804 randomized enrolled **“good risk” DCIS (size ≤ 2.5 cm, grade 1-2, margin ≥ 3 mm)** to whole breast radiation (RT) or none
 - ECOG-ACRIN E5194 enrolled 2 prospective observation cohorts without RT, one with the **same “good risk” characteristics as NRG/RTOG 9804**
- In both trials, the use of tamoxifen was optional but tracked.

Trials and Treatment Arms



	<u>NRG/RTOG 9804</u>			<u>ECOG-ACRIN E5194</u>			<u>COMBINED</u>	
	Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm		Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm	Cohort 1: Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm		Cohort 2: High-grade DCIS, tumor size ≤ 1 cm	Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm	
	Observ +/-Tamox		RT +/-Tamox	Observ +/-Tamox		Observ+/- Tamox	Observ +/-Tamox	
Analyzable	317		312	561		104	878	
Tam use	n	%		n	%		n	%
Yes	208	66		170	30		378	43
No	109	34		391	70		500	57

Trials and Treatment Arms

	<u>NRG/RTOG 9804</u>			<u>ECOG-ACRIN E5194</u>			<u>COMBINED</u>	
	Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm			Cohort 1: Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm			Low/intermediate-grade DCIS, tumor size ≤ 2.5 cm	
	Observ +/-Tamox		+	Observ +/-Tamox		=	Observ +/-Tamox	
Analyzable	317			561			878	
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Trials and Treatment Arms



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Methods



- A combined database from the non-RT arm of NRG/RTOG 9804 and the “good risk” cohort from ECOG-ACRIN E5194 was created.
- Distributions of patient and DCIS characteristics by tamoxifen use (yes vs. no) were compared using the Chi-square test.
- IBR, invasive IBR, DCIS IBR and contralateral breast event (CBE) were estimated by the cumulative incidence method and distributions between tamoxifen use were compared using Gray’s test.
- A 2-sided significance level of 0.05 was used.
- Univariate and multivariable Fine-Gray regression was used to analyze the effects of factors, in addition to tamoxifen use, that may be associated with endpoints.

Patient Characteristics

		Yes tamoxifen (n=378)	No tamoxifen (n=500)	Total (n=878)
Age (years)	Median (min-max)	58 (34-82)	61 (28-88)	59 (28-88)
	< 50	84 (22%)	91 (18%)	175 (20%)
	≥ 50	294 (78%)	409 (82%)	703 (80%)
	<i>p=0.14</i>			
Menopausal status				
	Pre-menopausal	87 (23.0%)	115 (23.0%)	202 (23.0%)
	Post menopausal/ Unknown	291 (77.0%)	385 (77.0%)	676 (77.0%)
	<i>p=1.00</i>			
Race	White	326 (86%)	454 (91%)	780 (89%)
	Non-white	52 (14%)	46 (9%)	98 (11%)
	<i>p=0.034</i>			

DCIS Characteristics

		Yes tamoxifen (n=378)	No tamoxifen (n=500)	Total (n=878)
Margin width (mm)	<3	6 (2%)	13 (3%)	19 (2%)
	≥3 - 9	189 (50%)	345 (69%)	534 (61%)
	≥10	80 (21%)	89 (18%)	169 (19%)
	Negative by negative re-excision	103 (27%)	53 (11%)	156 (18%)
	<i>p</i> <0.0001			
Pathologic size (mm)		(n=377)	(n=499)	(n=876)
	≤ 5	215 (57%)	206 (41%)	421 (48%)
	6-10	111 (29%)	199 (40%)	310 (35%)
	> 10	51 (13%)	94 (19%)	145 (17%)
	<i>p</i> <0.0001			
DCIS grade	Nuclear Grade 1	137 (36%)	135 (27%)	272 (31%)
	Nuclear Grade 2	202 (53%)	294 (59%)	496 (56%)
	Nuclear Grade 3/High	39 (10%)	71 (14%)	110 (13%)
	<i>p</i> =0.0034			

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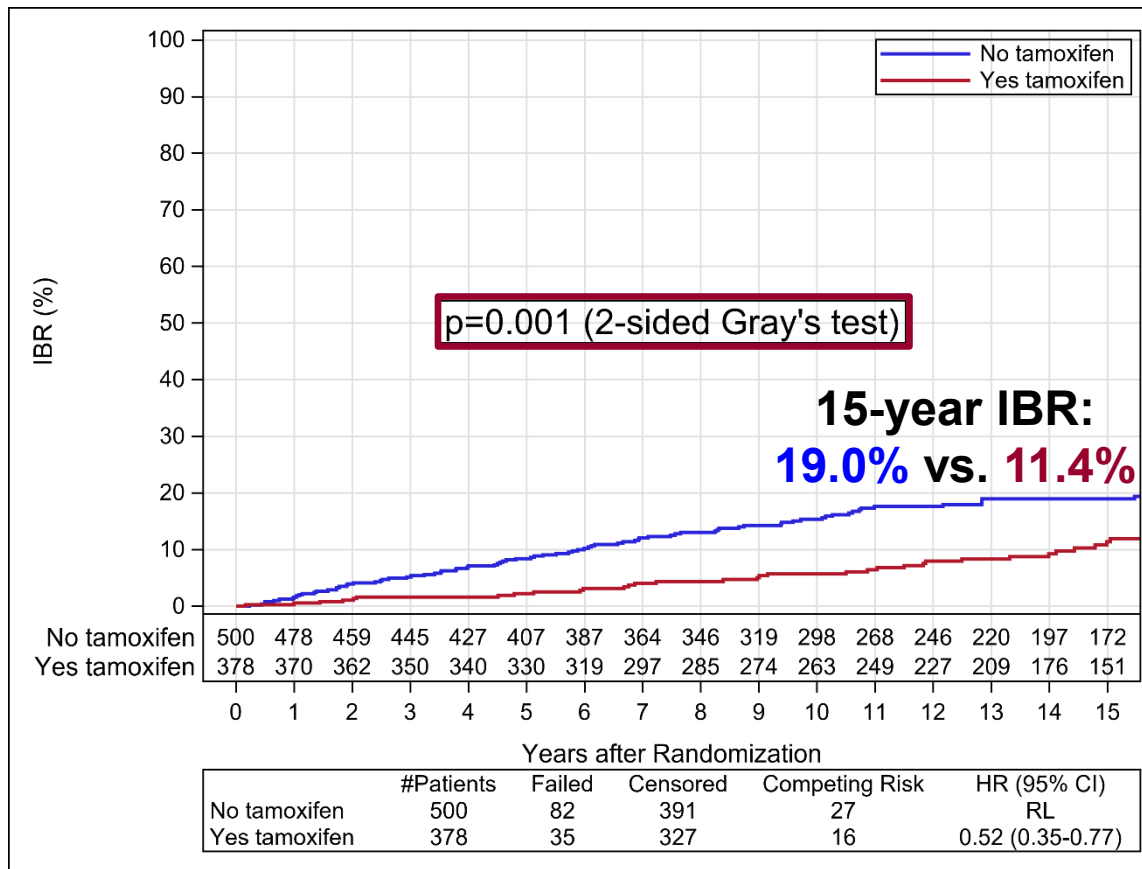
NRG ONCOLOGY  ECOG-ACRIN
cancer research group

NRG Oncology/RTOG 9804 and ECOG-ACRIN E5194

DCIS Characteristics

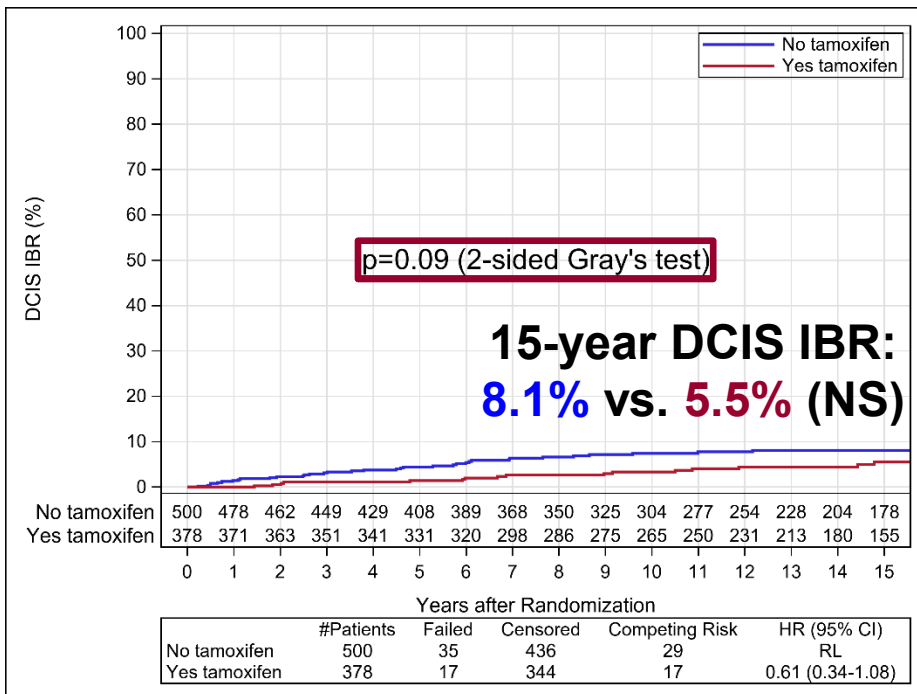
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Overall IBR by Tamoxifen Use

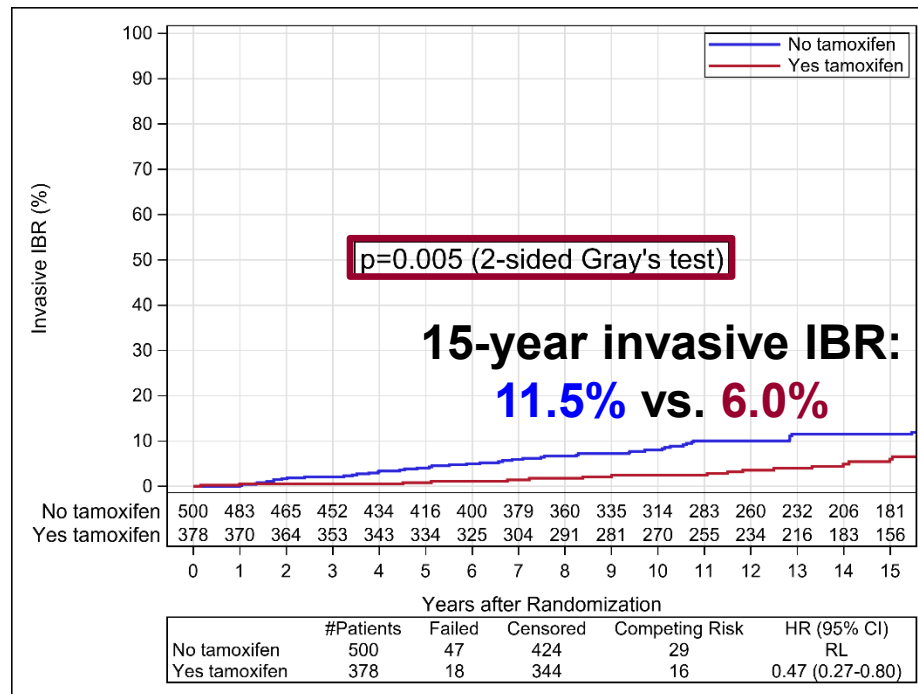


IBR by Tamoxifen Use

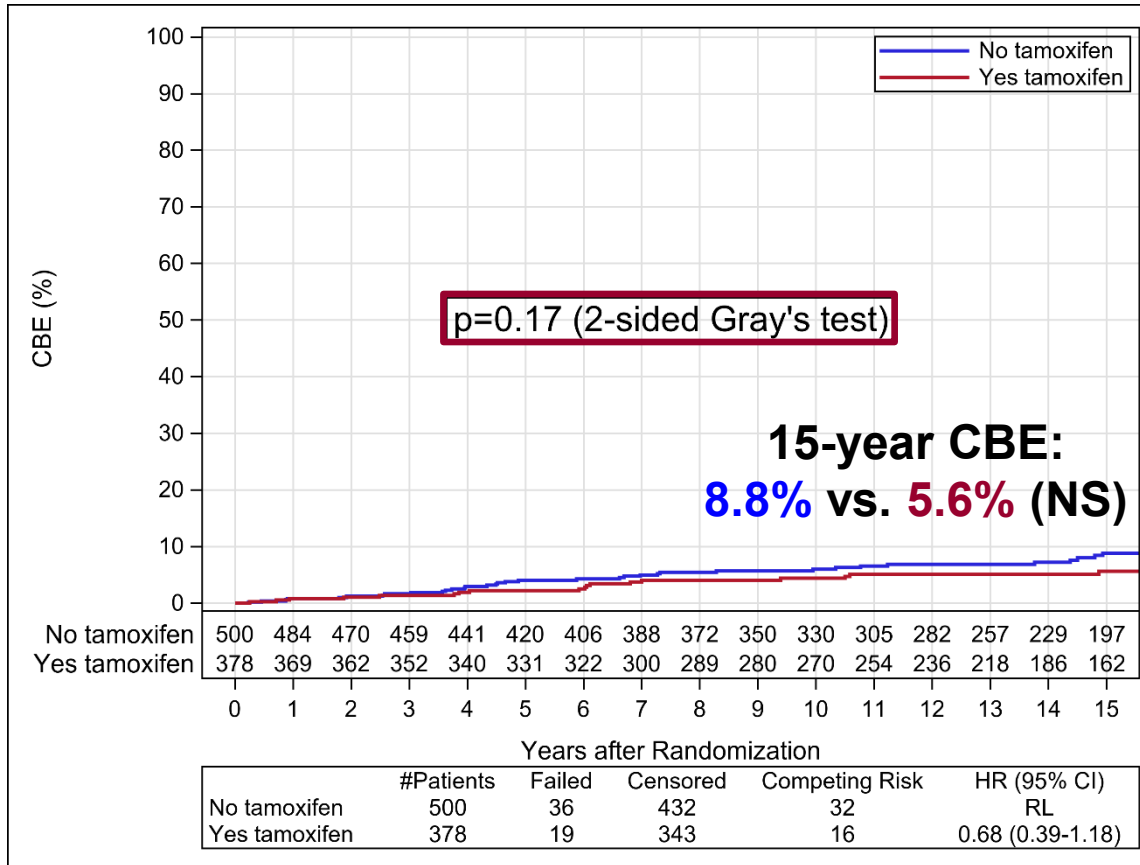
DCIS IBR by Tamoxifen Use



Invasive IBR by Tamoxifen Use



CBE by Tamoxifen Use



Univariate Fine-Gray Regression Analysis of IBR (117 events)

Variables	Comparison	HR	95% C.I.	p-value
Trial	NRG/RTOG 9804 (RL) vs. ECOG-ACRIN E5194	1.17	(0.79–1.72)	0.43
Age	continuous	1.00	(0.98-1.02)	0.76
Race	White (RL) vs. Non-white	0.81	(0.43-1.55)	0.53
Menopausal status	Post/Surgical/Unknown (RL) vs. Pre	1.23	(0.82-1.84)	0.32
Margin width	<3 mm/ Negative by negative re-excision (RL) vs. ≥ 3 mm – 9 mm	0.84	(0.54-1.30)	0.43
	<3 mm/ Negative by negative re-excision (RL) vs. ≥ 10mm	0.80	(0.45-1.40)	0.43
Pathologic size	≤ 5 mm (RL) vs. 6-10 mm	1.60	(1.05-2.44)	0.028
	≤ 5 mm (RL) vs. > 10 mm	2.52	(1.57-4.04)	0.0001
DCIS grade	NG1 (RL) vs. NG2	1.59	(1.02-2.50)	0.042
	NG1 (RL) vs. NG3/High	1.86	(1.04-3.32)	0.035

Multivariable Fine-Gray Regression Analysis

	Variables	Comparison	HR	95% C.I.	p-value
IBR* (events=117)	Tamoxifen use	No (RL) vs. Yes	0.56	(0.38–0.84)	0.0044
	Pathologic size	≤ 5 mm (RL) vs. 6-10 mm	1.48	(0.96-2.27)	0.073
		≤ 5 mm (RL) vs. > 10 mm	2.33	(1.45-3.75)	0.0005

*DCIS grade fell out of the model for IBR

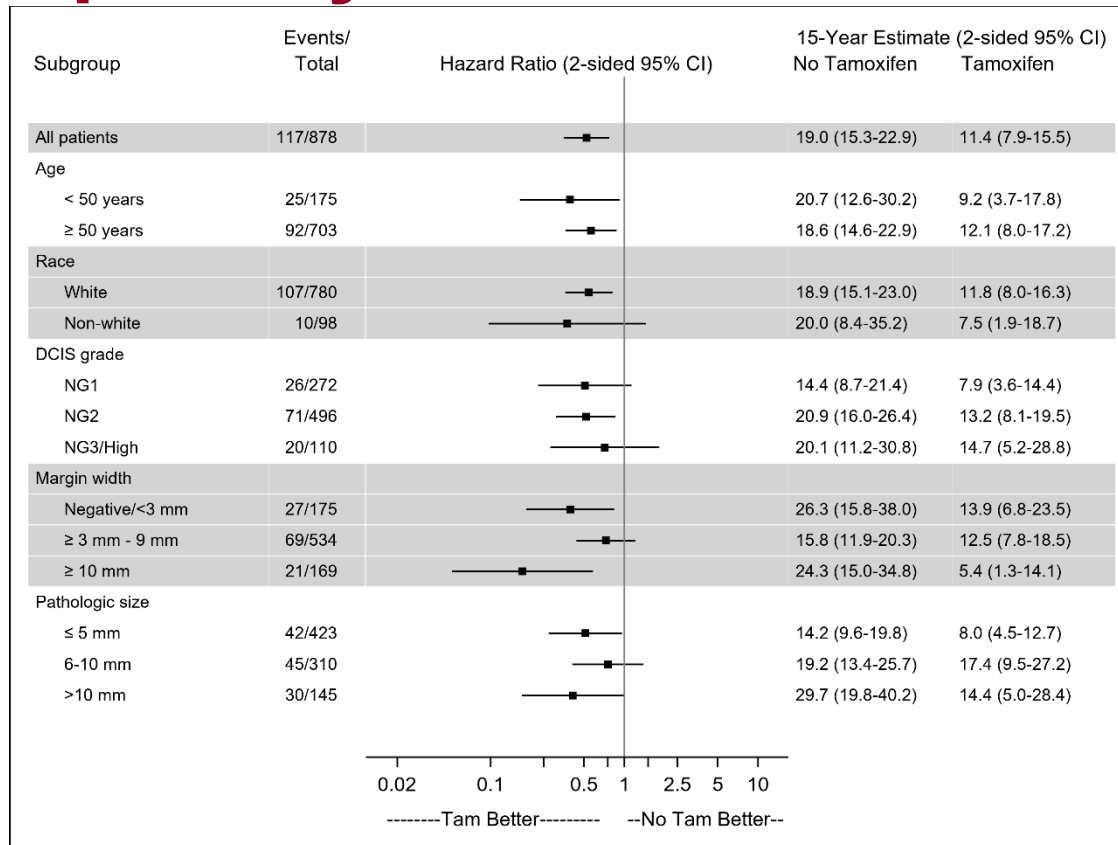
Multivariable Fine-Gray Regression Analysis

	Variables	Comparison	HR	95% C.I.	p-value
Invasive IBR* (events=65)	Tamoxifen use	No (RL) vs. Yes	0.49	(0.28–0.84)	0.0092
	DCIS grade	NG1 (RL) vs. NG2	1.96	(1.03-3.72)	0.041
		NG1 (RL) vs. NG3/High	2.05	(0.90-4.68)	0.087
DCIS IBR** (events=52)	Tamoxifen use	No (RL) vs. Yes	0.66	(0.37–1.18)	0.16
	Pathologic size	≤ 5 mm (RL) vs. 6-10 mm	1.23	(0.62-2.44)	0.56
		≤ 5 mm (RL) vs. > 10 mm	3.20	(1.66-6.18)	0.0005

*Pathologic size fell out of the model for invasive IBR

**DCIS grade fell out of the model for DCIS IBR

Subgroup Analyses for Overall IBR



Conclusions



- This ancillary exploratory analysis combining NRG/RTOG 9804 and E5194 trials demonstrated that in patients with “good risk” DCIS by clinical criteria treated without RT after BCS, adjuvant tamoxifen use reduced overall IBR (19% to 11%) and invasive IBR (11% to 6%), but not DCIS IBR or CBE.
- In the absence of a survival impact for adjuvant therapy, the decision to recommend endocrine therapy in the setting of RT omission remains a shared process between patient and physician.
- Ongoing study of molecular profiling to inform RT decisions should also evaluate the impact of endocrine therapy decisions particularly in those not receiving RT.

Acknowledgements



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