

VI ZOOM Journal Club 2016

Bologna, 17 Febbraio 2017

NH Hotel De La Gare

II Sessione - *Impatto della RT nei diversi
profili biomolecolari*

Moderatori: Luigia Nardone,
Antonella Baldissera

11.00 Rapporteur: Carmen De Santis

11.15 Discussant: Fiorenza De Rose

11.30 Caso clinico: Sonia Silipigni

11.45 Discussione



Associazione
Italiana
Radioterapia
Oncologica

Breast Cancer 2

Gene expression profiling in breast cancer: classification, prognostication, and prediction

Jorge S Reis-Filho, Lajos Pusztai

Breast cancer is now perceived as a heterogeneous group of different diseases characterised by distinct molecular aberrations, rather than one disease with varying histological features and clinical behaviour.

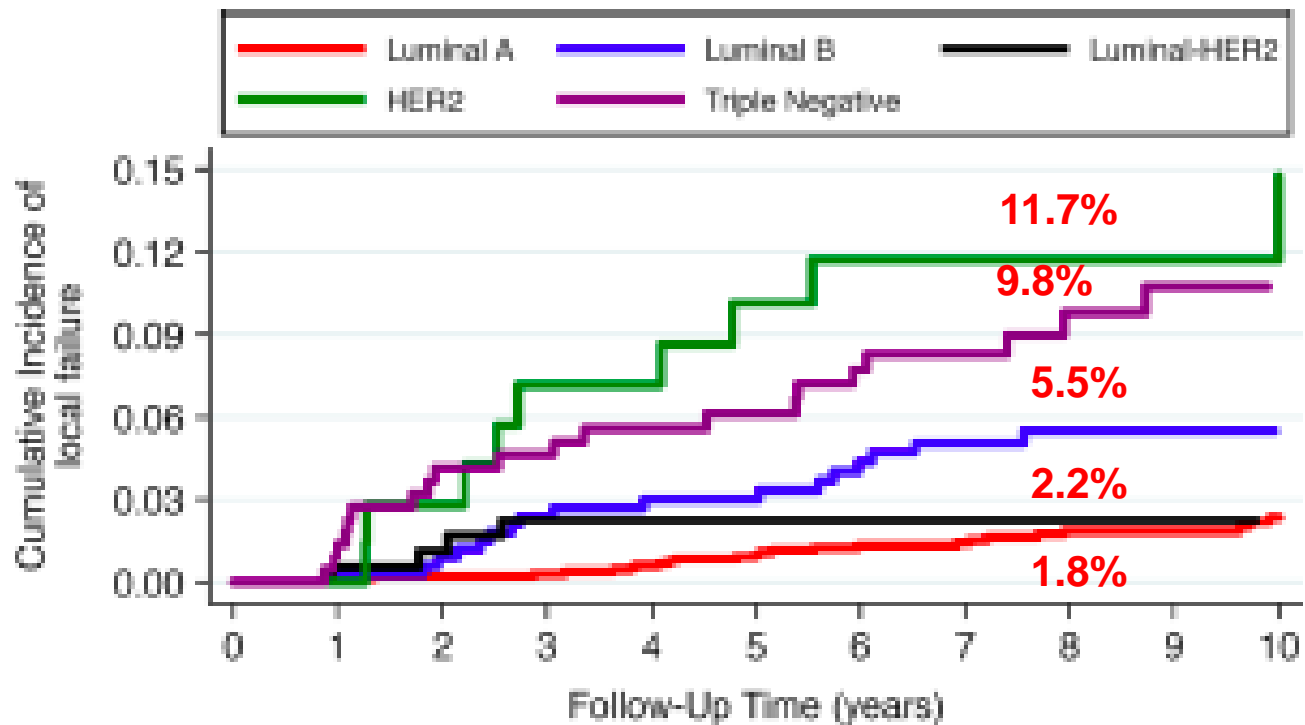
	Lum-A	Lum-B HER2-	Lum-B HER2+	HER2	TRIPLE NEGATIVE
LCR	99.1%	95.2%	95%	90.5%	89.6%
DFS	92.2%	80.1%	79%	77%	69.1%
DDFS	92.9%	82.2%	82.8%	83.3%	72.2%
OS	95.1%	88.7%	92.5%	85.6%	78.5%
ROS	100%	93.4%	96%	88.8%	80.1%

BRIEF REPORT

Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy

**Lior Z. Braunstein^{1,4} · Alphonse G. Taghian² · Andrzej Niemierko² ·
Laura Salama² · Alexander Capuco³ · Jennifer R. Bellon³ · Julia S. Wong³ ·
Rinaa S. Punglia³ · Shannon M. MacDonald² · Jay R. Harris³**

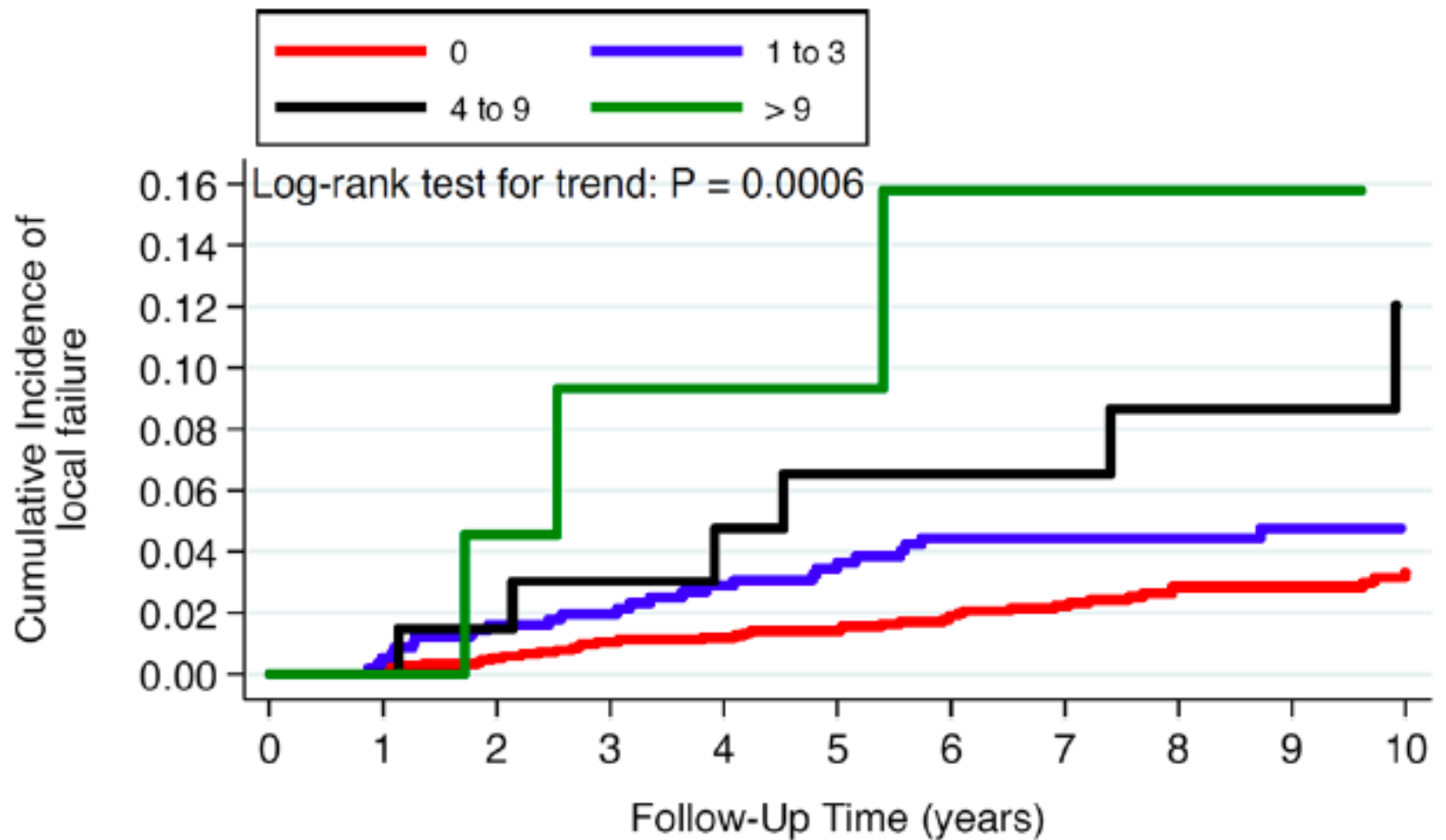
**2233 pts; median FUP 106 months
1998-2007**



Number at risk

Luminal A	1400	1380	1359	1334	1299	1250	1180	1030	823	668	539
Luminal B	351	347	333	319	307	298	278	238	193	161	128
Luminal-HER2	186	185	174	171	168	155	147	125	101	86	75
HER2	72	72	68	63	62	57	55	50	48	42	28
Triple Negative	994	917	909	896	888	878	868	843	809	766	73

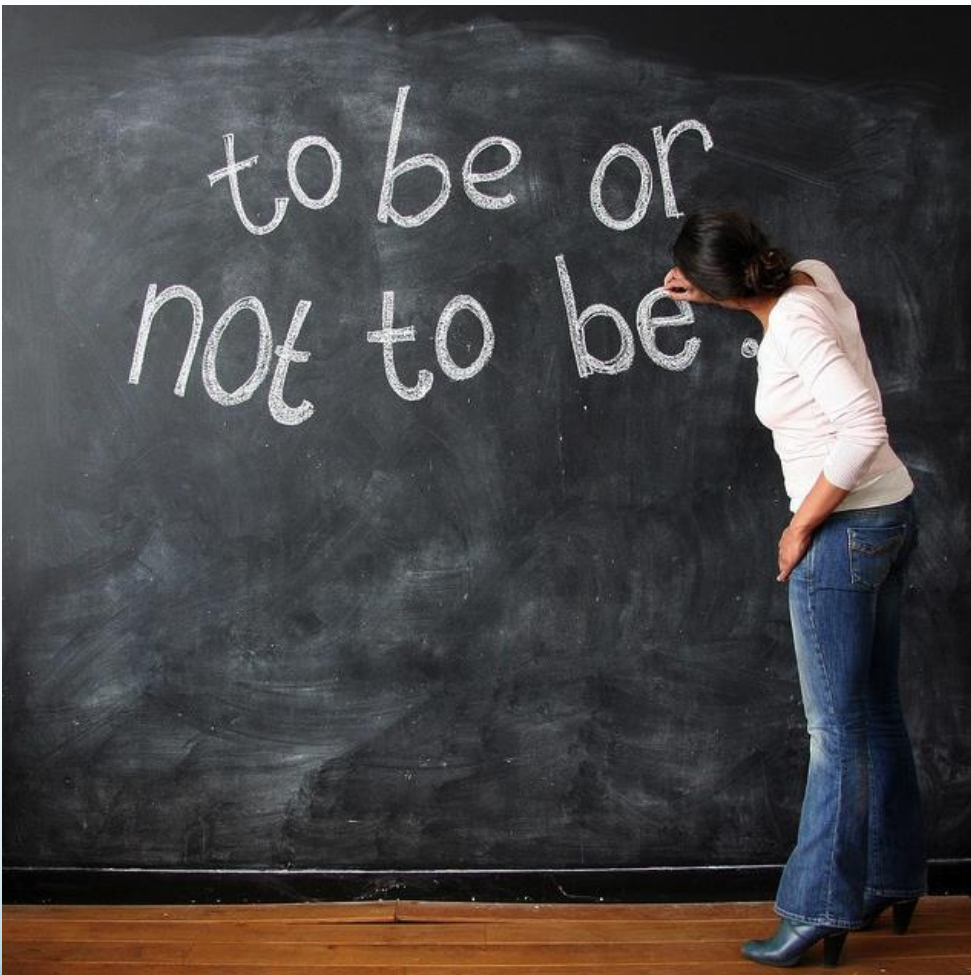
Fig. 1 Unadjusted Kaplan–Meier estimate of local recurrence by biologic subtype



Number at risk

0	1563	1545	1506	1469	1431	1374	1288	1106	883	720	585
1 to 3	576	564	547	536	519	498	477	423	345	283	230
4 to 9	70	68	64	60	55	52	50	47	38	31	25
> 9	24	24	20	18	15	14	13	10	8	7	3

Fig. 3 Unadjusted Kaplan–Meier estimate of local recurrence by number of involved lymph nodes



***INTENSIFY
OR
DEINTENSIFY***

- DESCALATING

- ① LUMINAL A DISEASE

- ② DCIS

- ESCALATING

- ③ TRIPLE NEGATIVE DISEASE

- ④ NODAL POSITIVE DISEASE

RT: 40 Gy in 16 fraz
+
Boost: 12.5 Gy in 5 fraz

Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy

Fei-Fei Liu, Wei Shi, Susan J. Done, Naomi Miller, Melania Pintilie, David Voduc, Torsten O. N. Sharon Nofech-Mozes, Martin C. Chang, Timothy J. Whelan, Lorna M. Weir, Ivo A. Olivotto, David R. McCready, and Anthony W. Fyles

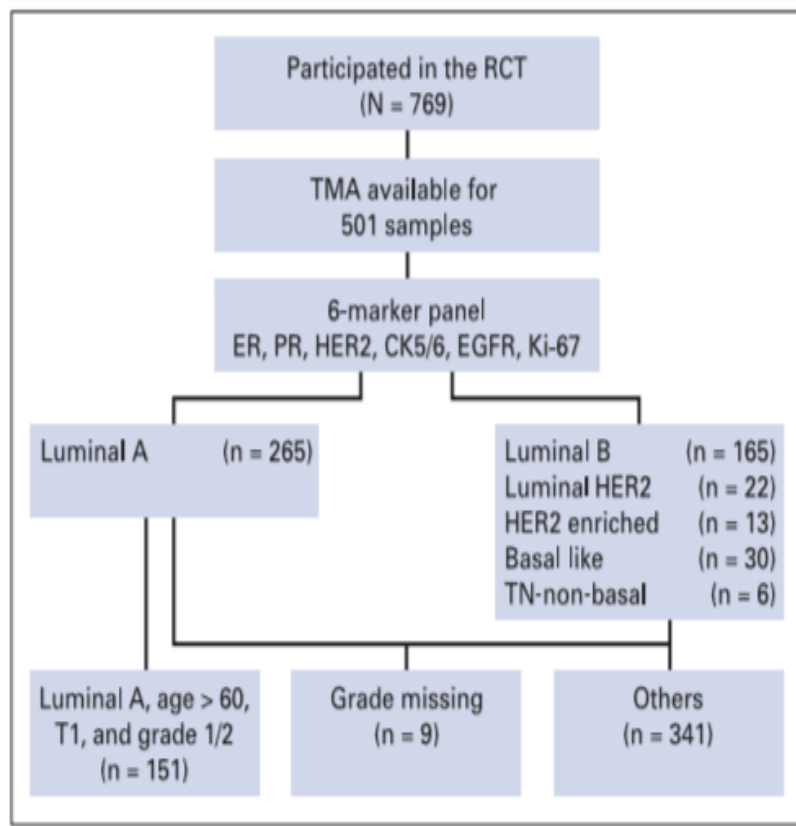


Table 1. Distribution of Clinicopathologic Characteristics

Characteristic	Patients (n = 501)	HR	P
Age, years			
50-60	130 (26%)		
> 60	371 (74%)		
Tumor size, cm*			
< 2	346 (69%)		
2-5	153 (31%)		
Grade†			
1 to 2	365 (77%)		
3	109 (23%)		
Treatment			
Tamoxifen + RT	257 (51%)		
Tamoxifen	244 (49%)		
Subtype			
Luminal A	265	5.2	
Luminal B	165	10.5	
Other	71	21.3	< .001

*Two samples were missing information about tumor size.

†Twenty-seven samples were missing information about grade.

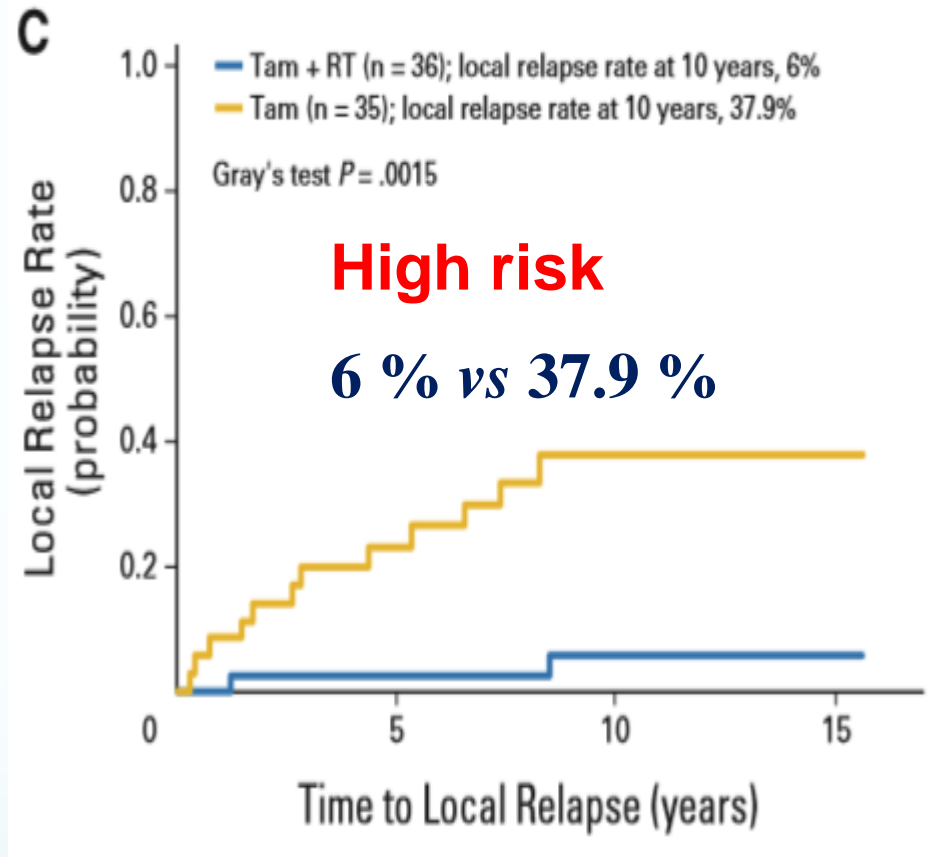
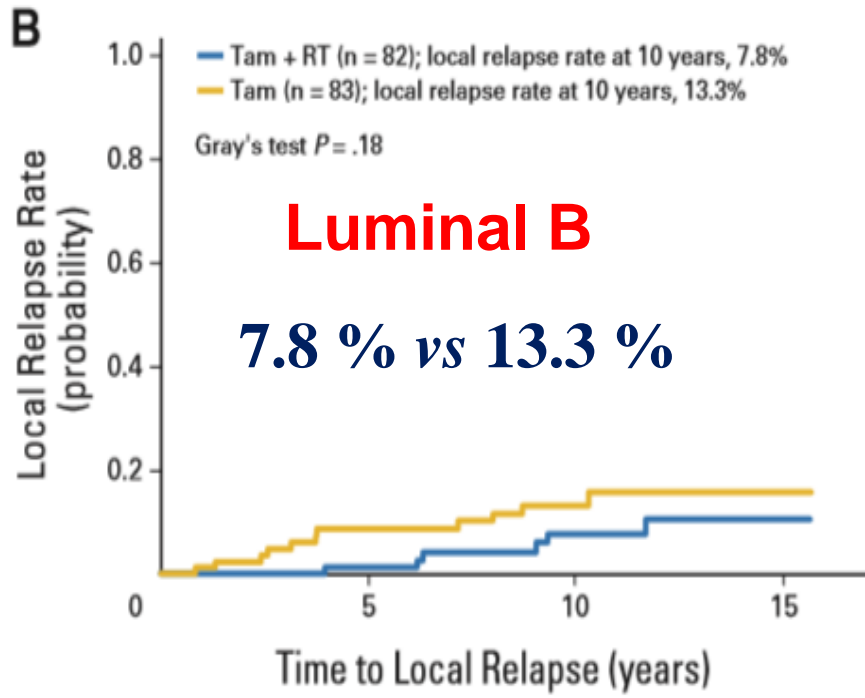
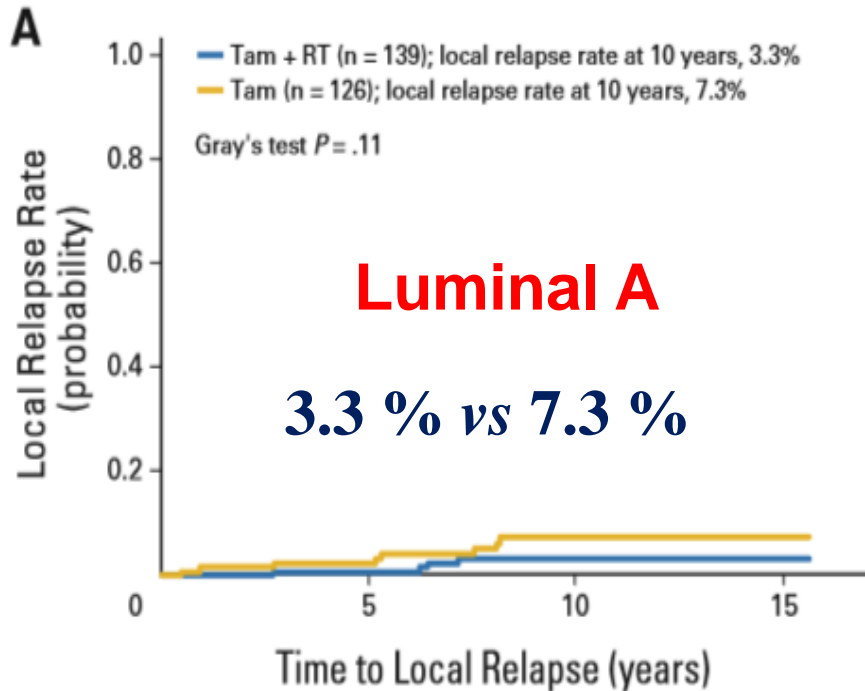


Table A5. Comparison of IBR Using the Clinical Models and Subtype Including Treatment Effects

Risk Group	No.	IBR at 10 Years (%)	95% CI	P
LR clinical luminal A	151	3.1	1.2 to 8.2	
High-risk clinical/subtype	341	11.8	8.6 to 16.1	.0063
LR clinical luminal A				
Tamoxifen + RT	77	5.0	1.6 to 15.0	
Tamoxifen	74	1.3	0.2 to 9.1	.42

Abbreviations: IBR, ipsilateral breast relapse; LR, low risk; RT, radiotherapy.

Luminal A Low-risk:

- ✓ Age > 60 years
- ✓ T1
- ✓ G1-G2

Table 4. Multivariable Analysis of IBR Adding the Clinical Risk Groups to Treatment and Intrinsic Subtype (significant variables shown)

Covariate	HR	95% CI	P
Tamoxifen + RT v tamoxifen	0.31	0.16 to 0.62	< .001
Clinical risk groups	2.2	1.1 to 4.4	.025
Luminal A v high risk	0.25	0.11 to 0.56	< .001
Luminal B v high risk	0.51	0.24 to 1.05	.068
Luminal A v luminal B	0.50	0.24 to 1.05	.069
Overall			.0033

Abbreviations: HR, hazard ratio; IBR, ipsilateral breast relapse; RT, radiotherapy.

IHC subtyping was prognostic for IBR but was not predictive of benefit from RT. Further studies may validate the exploratory finding of a low-risk luminal A group who may be spared breast RT.

Table 4

Reduction of ipsilateral breast tumour recurrences after radiotherapy in different subgroups.

Factor	Cumulative incidence of IBTR, %		Difference % (95% CI)
	Control <i>N</i> = 587	Radiotherapy <i>N</i> = 591	
All patients	23.9	11.5	12.4 (8.2, 16.6)
Age group, years			
≤49	28.0	19.8	8.2 (−1.7, 18.1)
50–59	24.0	13.2	10.8 (3.2, 18.4)
60–69	23.8	9.0	14.8 (8.5, 21.1)
≥70	16.7	2.8	13.9 (5.4, 22.4)
Screening detection			
No	27.4	11.6	15.8 (8.8, 22.8)
Yes	22.0	11.5	10.5 (5.5, 15.5)
Tumour size, mm			
≤10	26.2	12.0	14.2 (7.5, 20.9)
11–15	22.7	10.6	12.1 (5.4, 18.8)
16–20	23.7	11.8	11.9 (2.3, 21.4)
≥21	17.9	9.1	8.8 (−2.6, 20.2)
ER status			
Positive	26.1	9.9	16.2 (10.8, 21.6)
Negative	19.0	11.7	7.3 (−2.6, 17.2)
Unknown	21.7	14.4	7.3 (−0.8, 15.5)

IBTR, ipsilateral breast tumour recurrence; CI, confidence interval.

Table 1 Patient and tumor characteristics

Patient and tumor characteristics	<i>N</i> (%)
Age (yrs)	
Mean	64
Range	41–86
Laterality	
Left-sided	254 (52)
Right-sided	229 (46)
Histology	
Ductal carcinoma	350 (70)
Lobular carcinoma	63 (12)
Tubular carcinoma	26 (5)
Other	64 (13)
Tumor size (mm)	
Mean	13
Range	1–30
Pathological tumor stage	
pT1a	35 (7)
pT1b	158 (32)
pT1c	258 (51)
pT2	52 (10)
Pathological nodal stage	
pN0	397 (79)
pN1	84 (17)
pNx	2 (4)
Grading	
G1	224 (45)
G2	232 (46)
G3	47 (9)

Table 2 Treatment characteristics

Treatment characteristics	<i>N</i> (%)
Radiotherapy schedule	
46 Gy/20 fractions	378 (75)
40.05 Gy/15 fractions	125 (25)
Chemotherapy	
Yes	75 (15)
No	418 (85)
Type of chemotherapy (75 pts)	
FEC	13 (18)
AC	37 (49)
TC	22 (29)
Other	3 (4)
Hormonal therapy	
Yes	466 (95)
No	27 (5)
Type of hormonal therapy (466 pts)	
Tamoxifen	146 (31)
Aromatase inhibitor	320 (69)
Trastuzumab	
Yes	27 (5)
No	466 (95)
Biological type	
Luminal A	369 (73)
Luminal B	83 (17)
HER2-like	32 (6)
Triple negative	19 (4)

Table 4 Clinical predictors of local failure

Variable	HR	SE	z	95 % CI	p
Age	0.97	0.119	-0.20	0.767-1.242	0.844
Tumor stage (pT2 vs. pT1)	27.71	41.001	2.25	1.525-503.6	0.025
Nodal stage (pN1 vs. pN0)	13.09	21.146	1.59	0.552-310.4	0.111
Grading (G3 vs. G1-G2)	6.92	9.089	1.47	0.527-90.8	0.141
Ki-67 (>14 vs. <14 %)	1.06	0.041	1.60	0.986-1.148	0.109
Hormonal status (pos vs. neg)	0.922	0.034	-2.18	0.858-0.991	0.029
Hormonal therapy (yes vs. no)	196.5	607.1	1.71	0.460-8384	0.087
Chemotherapy (yes vs. no)	0.16	0.314	-0.93	0.003-7.707	0.353
Triple negative (no vs. yes)	0.02	0.078	-1.31	0.001-5.764	0.190

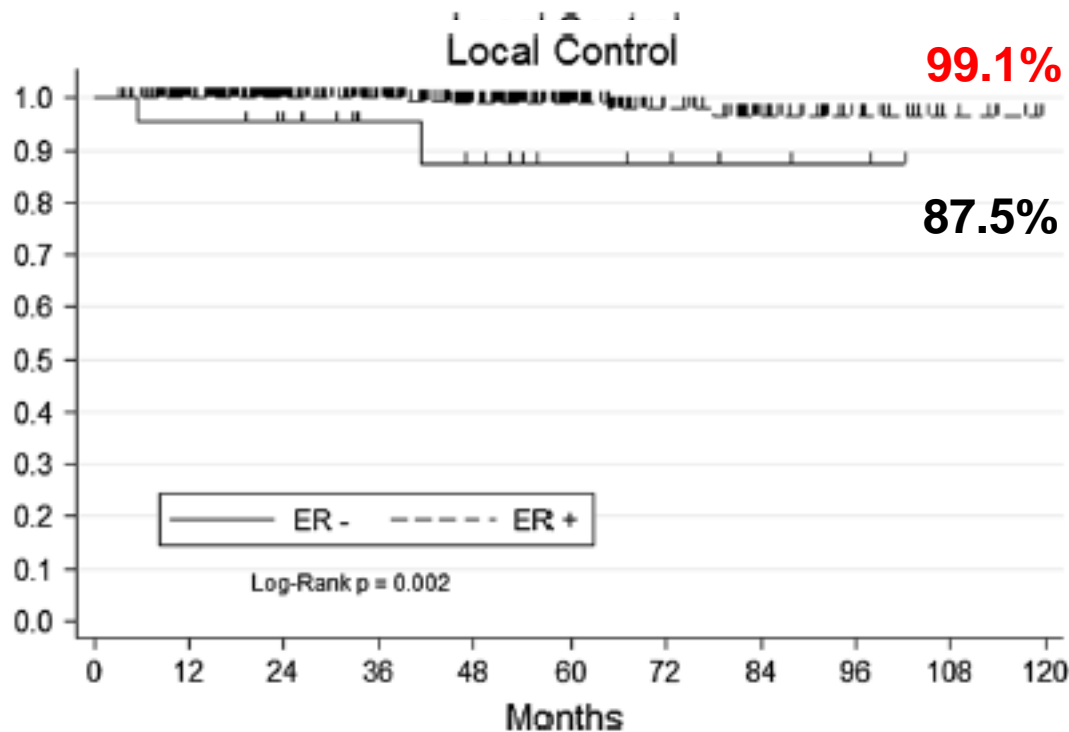


Fig. 3 Local control according to hormonal status

HF, with no boost delivered, is a safe and effective option for a population of low-risk breast cancer. A subgroup of patients with larger tumors and/or with no estrogen receptor expression may potentially benefit from treatment intensification with a boost dose to the lumpectomy cavity.

- DESCALATING

- ① LUMINAL A DISEASE

- ② DCIS

- ESCALATING

- ③ TRIPLE NEGATIVE DISEASE

- ④ NODAL POSITIVE DISEASE

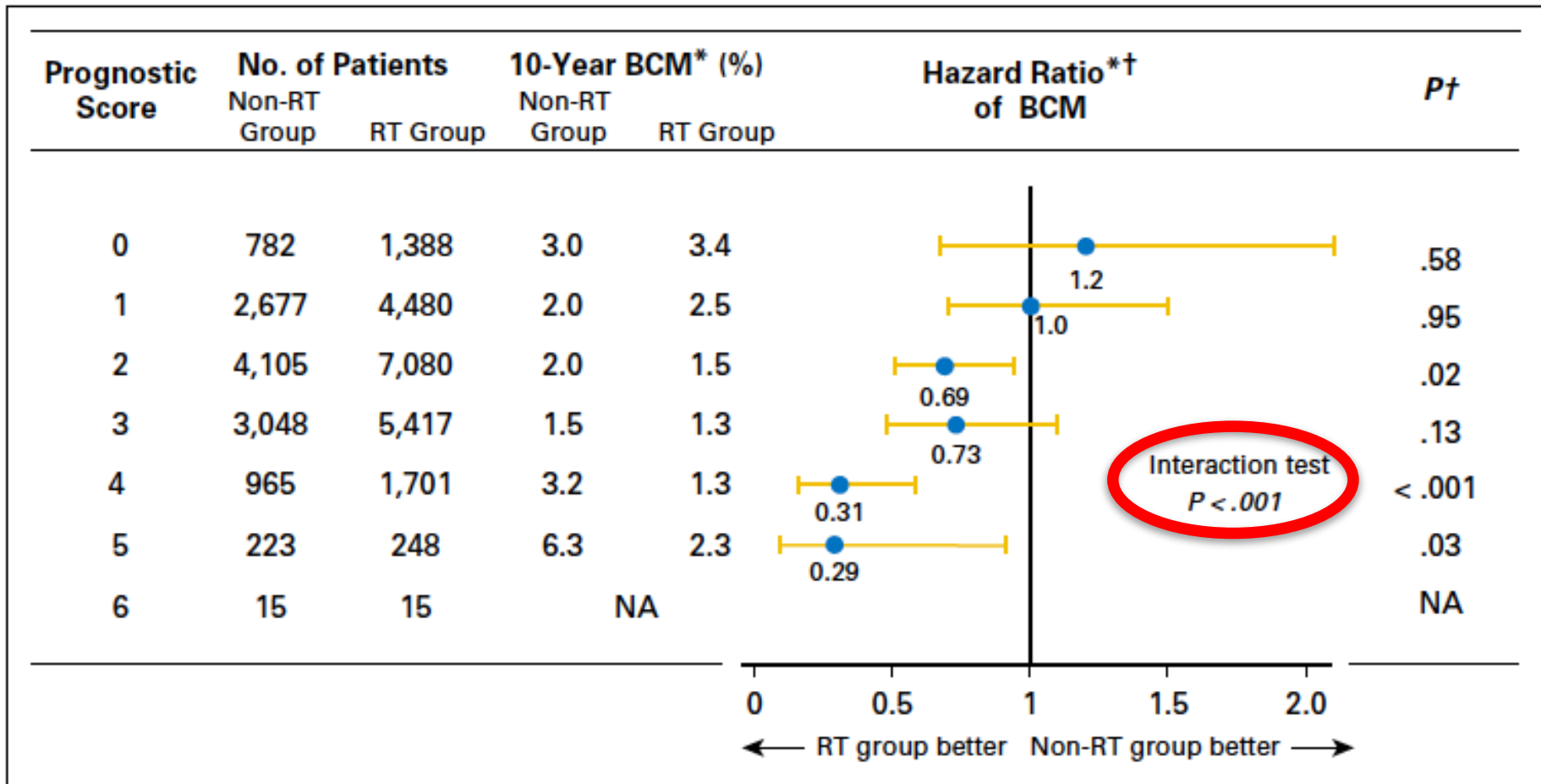
Patient Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ: A Population-Based Longitudinal Cohort Study

ong, Fatih Aydogan,

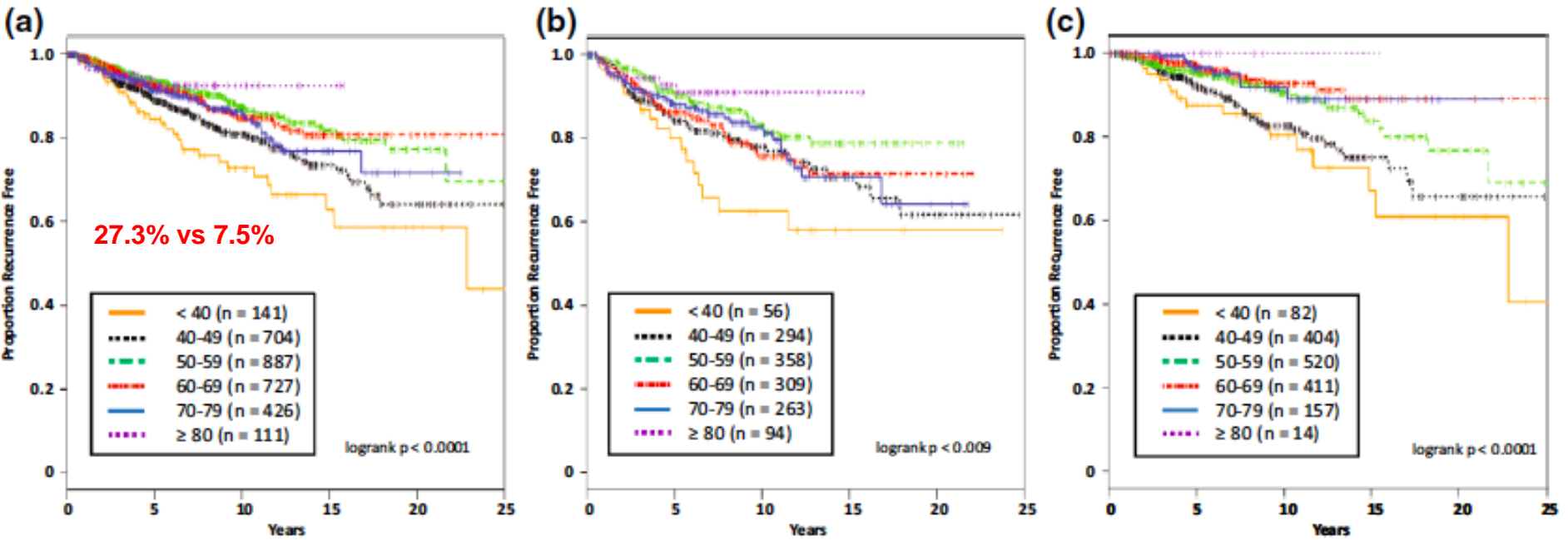
	Age (years)	Size (mm)	Histology	
Points				Score
0	61+	< 16	Low grade	0
1	40-60	16-40	Intermediate grade	
2	< 40	41+	High grade	6

A vertical arrow on the right side of the table points downwards from the score 0 row to the score 6 row, indicating that the score increases as the patient characteristics move from the top row to the bottom row.

Fig 1. Patient prognostic score: risk stratification. Modified from Smith et al.²⁰

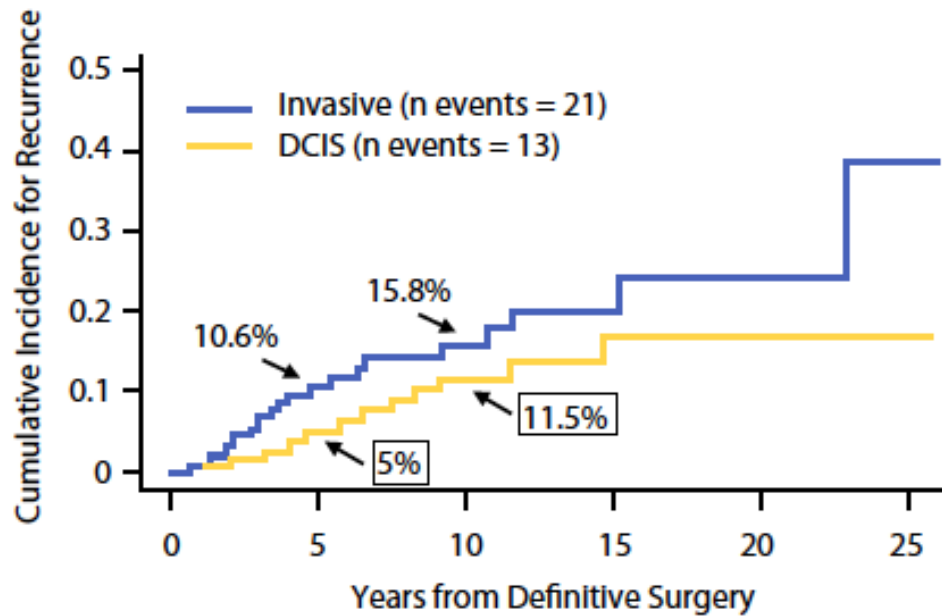


RT improves survival in patients with higher NG, age younger than 60 years and tumor size > 1,6 cm.

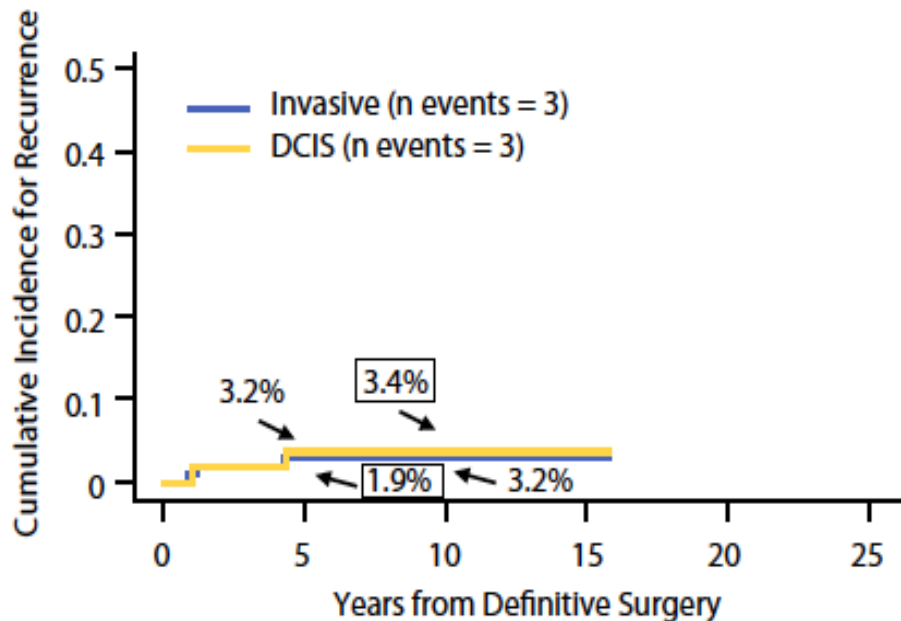


2996 pts 1978-2010

(a) Age < 40 (n = 141)



(f) Age ≥ 80 (n = 111)



Women < 40 years of age were empirically at higher risk for invasive recurrence than DCIS recurrence (10-year invasive vs. DCIS risk: 15.8 vs. 11.5 %). In contrast, in all other age groups the risk of DCIS recurrence was at least as high as the risk of invasive recurrence.

For both invasive and in situ recurrences, the use of RT was associated with an approximate 50 % reduction in the risk of recurrence ($p < 0.00004$).

- DESCALATING

- ① LUMINAL A DISEASE

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Original Study

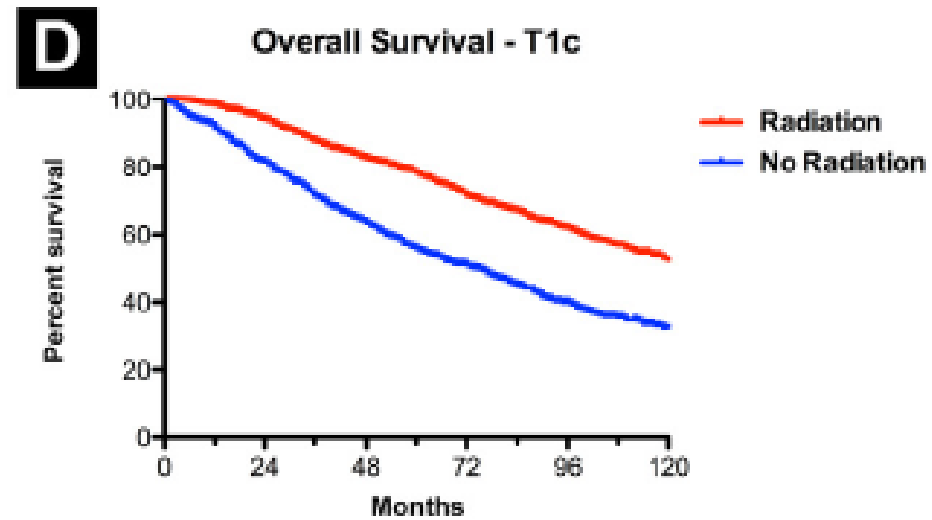
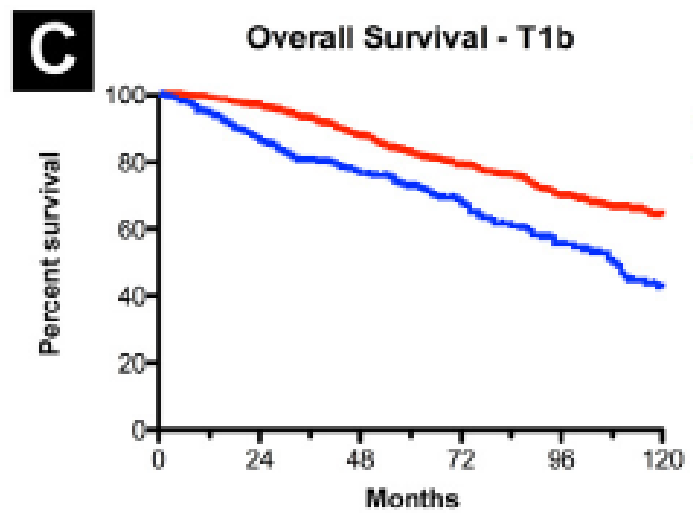
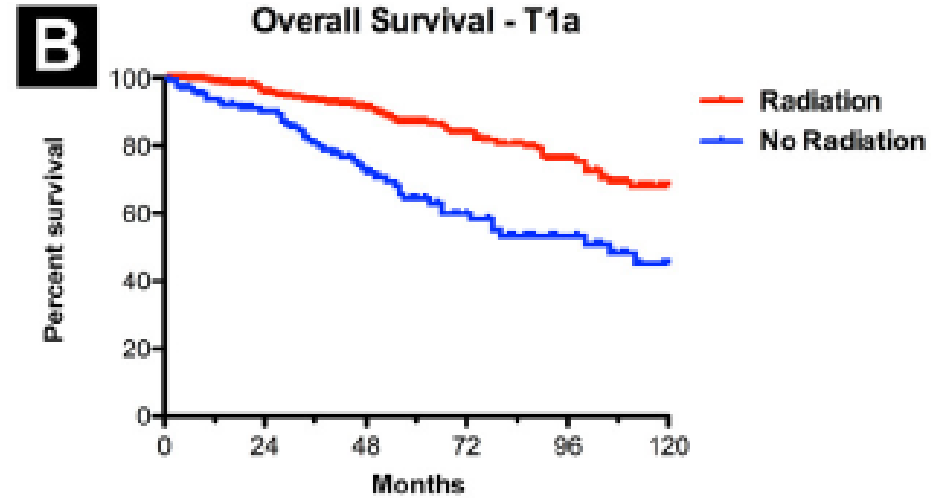
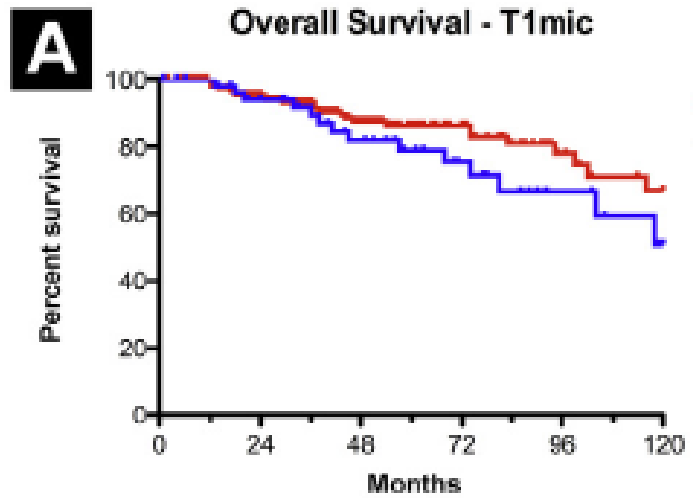


Table 3 Univariate Analysis of Survival Outcomes

	Overall Survival			Cancer-Specific Survival		
	Hazard Ratio	95% CI	<i>P</i>	Hazard Ratio	95% CI	<i>P</i>
Age	1.111	1.099-1.123	<.0001	1.069	1.048-1.090	<.0001
Race			.101			.483
White	Reference			Reference		
Black	1.114	0.938-1.321		1.190	0.876-1.617	
Other	0.775	0.574-1.046		0.904	0.540-1.515	
Grade			.037			.0002
1	Reference			Reference		
2	1.199	0.960-1.499		2.097	1.182-3.719	
3	1.323	1.068-1.638		2.890	1.657-5.041	
4/undifferentiated	1.131	0.764-1.676		3.182	1.475-6.965	
PR status			.856			.253
PR ⁺	Reference			Reference		
PR ⁻	0.983	0.813-1.188		1.265	0.844-1.894	
Laterality			.3883			.236
Left	Reference			Reference		
Right	0.957	0.865-1.058		0.893	0.739-1.076	
T-stage			<.0001			<.0001
T1mic	Reference			Reference		
T1a	1.155	0.806-1.654		1.476	0.638-3.412	
T1b	1.246	0.900-1.726		1.633	0.755-3.532	
T1c	1.895	1.381-2.599		3.583	1.694-7.576	
Radiation	2.073	1.869-2.297	<.0001	2.030	1.798-2.633	<.0001

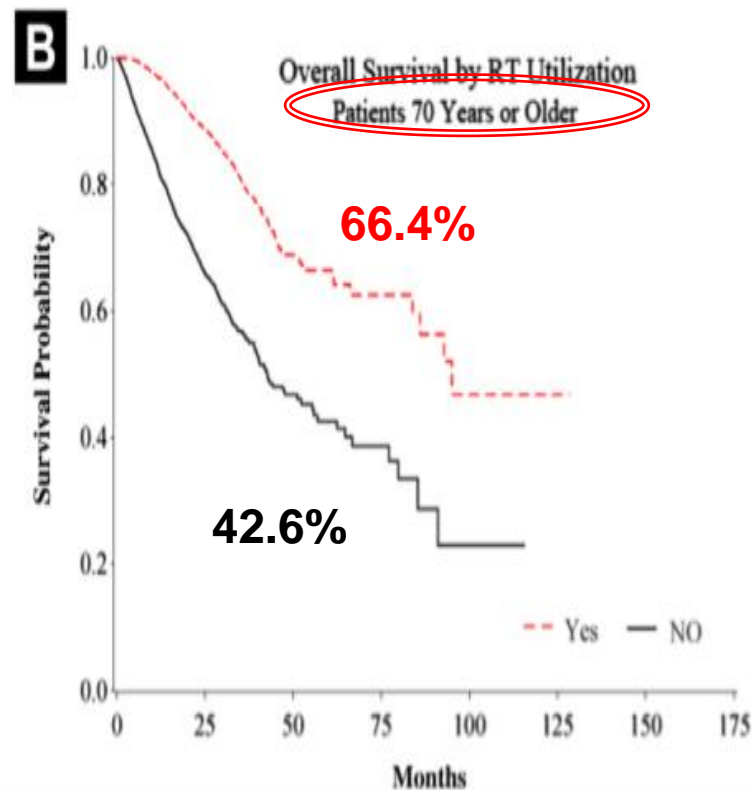
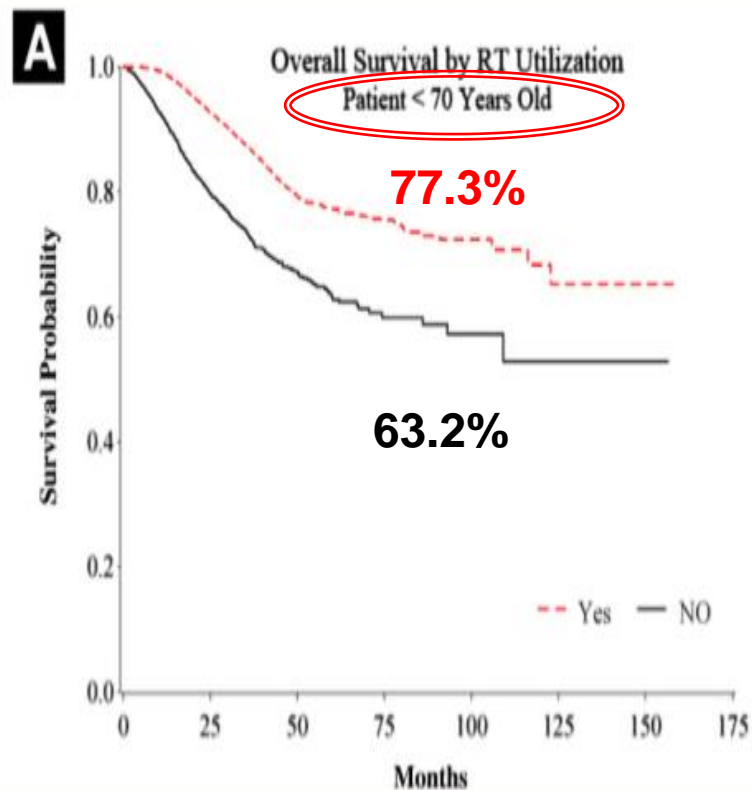
Radiotherapy in Patients 70 Years and Older With Triple-Negative Breast Cancer

Ozer Algan,¹ Yan D. Zhao,² Terence Herman¹

Table 5 Studies Evaluating Postoperative RT in Setting of Triple-Negative Breast Cancer

Study	n	Follow-up	LRR (No RT)	LRR (RT)	RFS (No RT)	RFS (RT)	OS (No RT)	OS (RT)
Wang (2011) ¹⁴	681	86.5 months			74.6% (5 years)	88.3% ^a (5 years)	78.7% (5 years)	90.4% ^a (5 years)
Kyndi (2008) ¹⁵	1000	17 years (204 months)	32%	15% ^a			32%	39%
Bayoumi (2014) ¹⁶	111	64 months (5-year results)	29.5% (5-year LR)	Versus 7% (5-year LR)	82%	94% ^a	51%	65% (<i>P</i> = .09)
Current Study								
All	44,731						56.7	75.5 ^a
Age <70 years	34,647						63.2	77.3 ^a
Age ≥70 years	10,079						42.6	66.4 ^a

44731 pts 1998-2012; median age 59 (19-90);5570 >70 aa



Conclusion: In this group of high-risk patients, there was decreased use of RT in older patients. In our study of a large patient population with TNBC, RT was associated with increased OS rates in both younger and older patients, and RT should be strongly considered, when indicated by clinicopathologic factors, in patients with TNBC.

The results of our study demonstrate a continued role for RT in older patients diagnosed with TNBC.

- DESCALATING

- ① LUMINAL A DISEASE

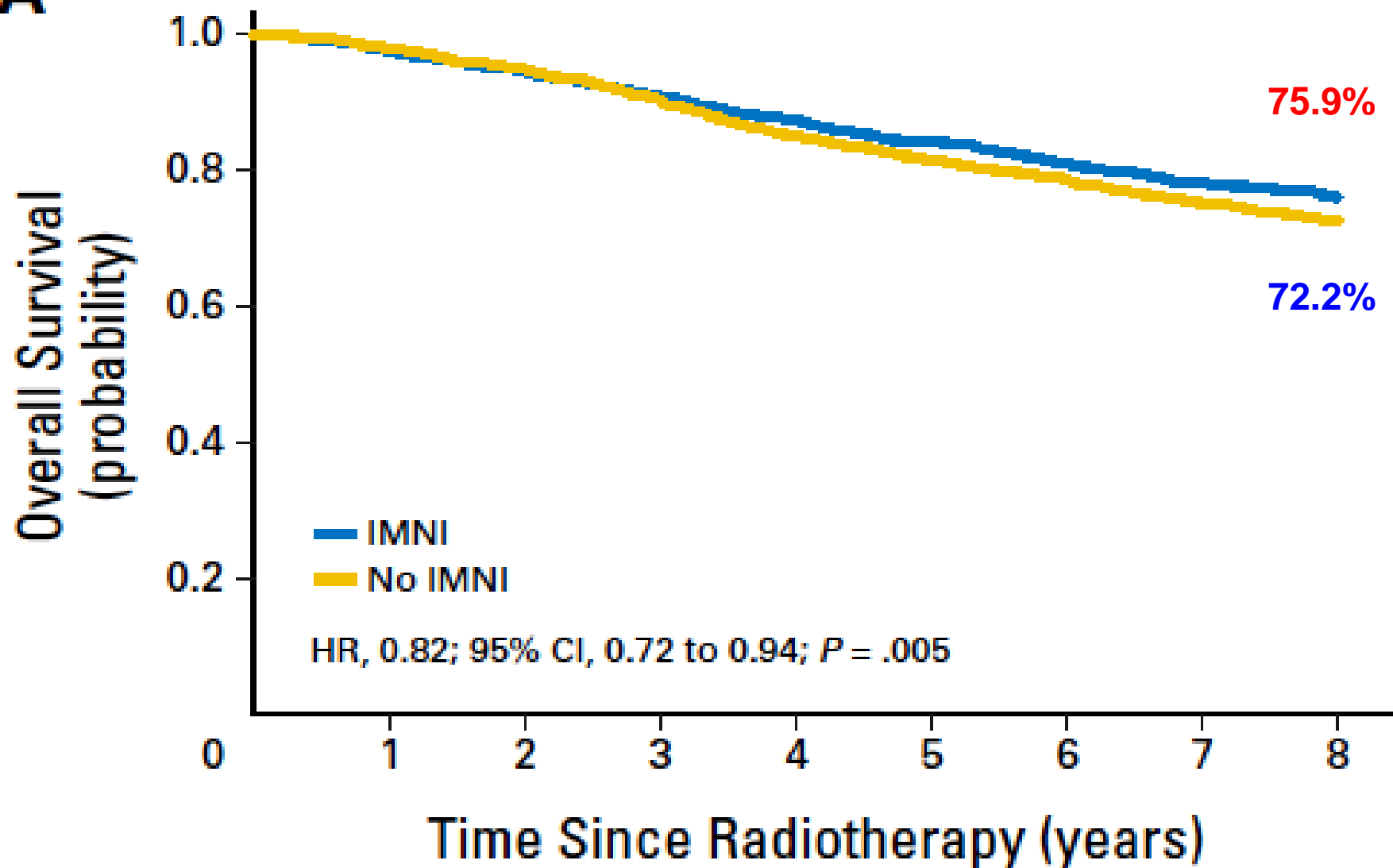
- ② DCIS

- ESCALATING

- ③ TRIPLE NEGATIVE DISEASE

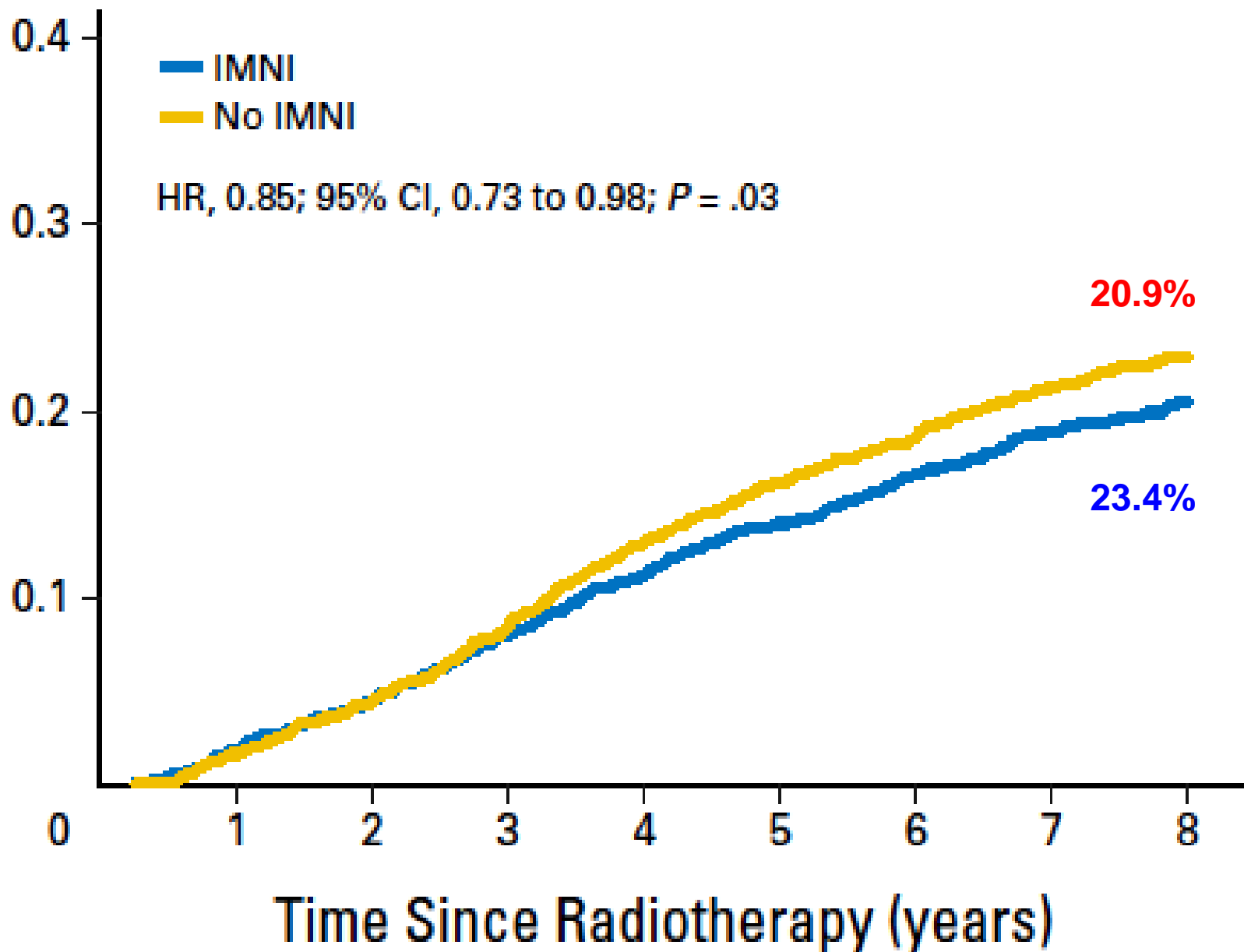
- ④ NODAL POSITIVE DISEASE

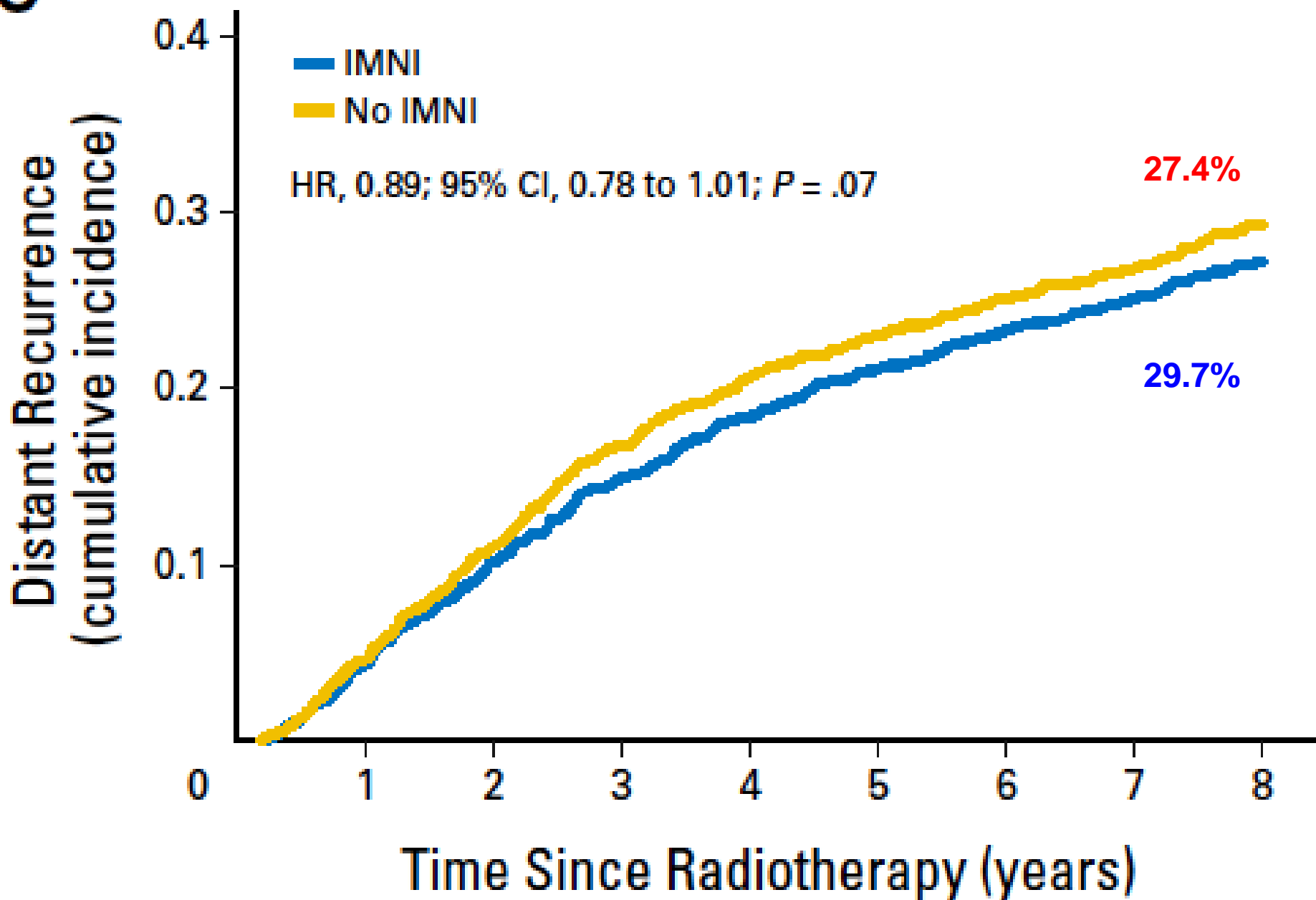
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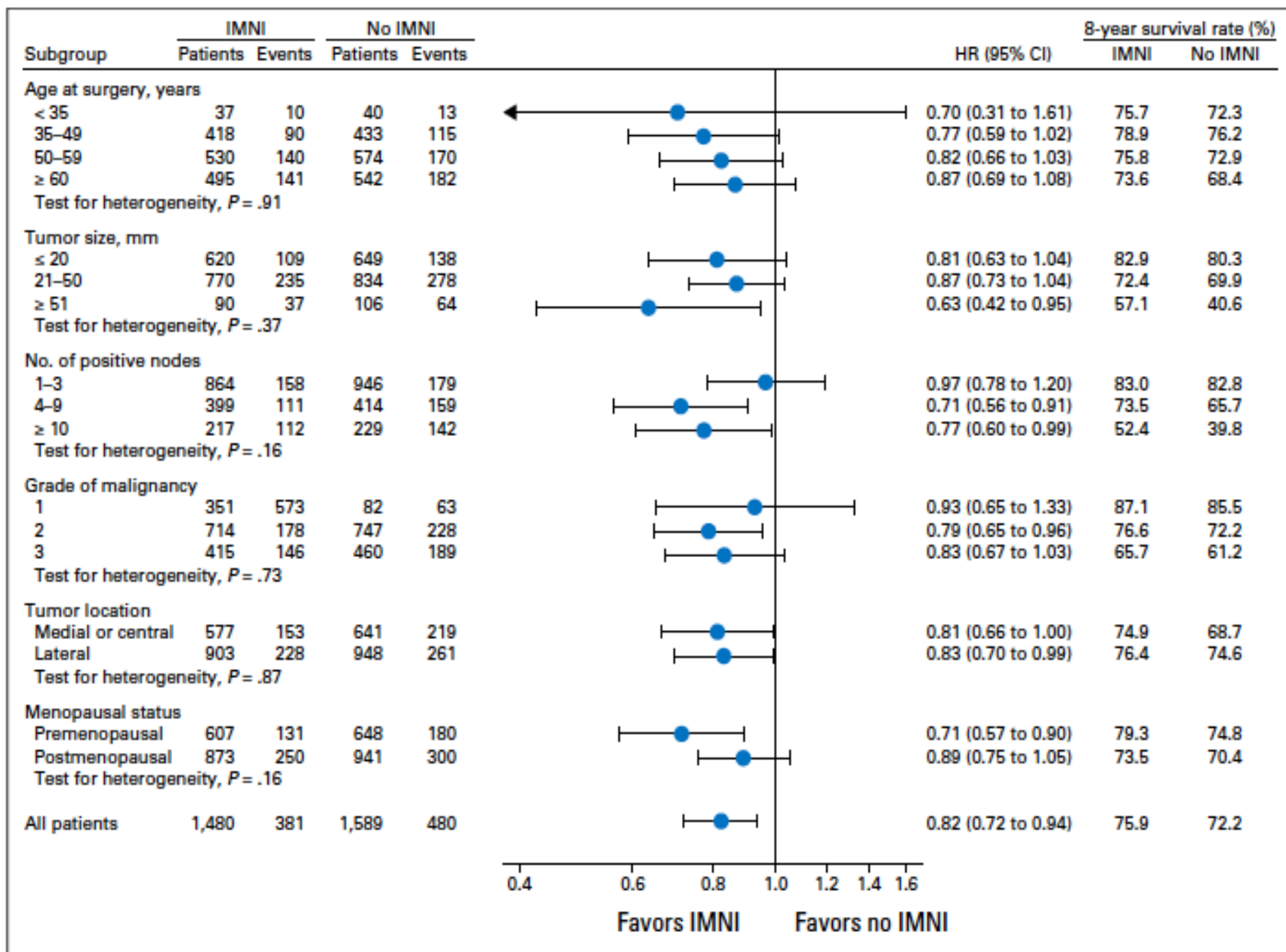


No. at risk

IMNI	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,512	1,356	1,248	791

B**Breast Cancer Mortality
(cumulative incidence)**

C



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The Breast

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- **The time is ripe to make radiotherapy full adaptive by embracing the biological behaviour of tumours, considering their different potential and pathways for recurrence**

- **More personalized radiotherapy must replace the approach of “one size only”**
From technological advances to biological understanding: The main steps toward high-precision RT in breast cancer



- **Current knowledge derived from studies based mainly on pathology rather than on biology, makes it difficult to adapt treatment to the individual patient**

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^c Medical Physics Unit, European Institute of Oncology, Milan, Italy

^d Scientific Directorate, European Institute of Oncology, Milan, Italy

Table 2

Summary of radiosensitivity and pattern of recurrence. Molecular classifications of breast cancers are based on immunohistochemistry. Suggestion for therapeutic approaches is indicative. Decision –making for radiation techniques and volumes must integrate biological, clinical and pathological factors. True: any reappearance in the same quadrant as the primary tumour; Elsewhere: any reappearance of carcinoma in other quadrants; RT: radiotherapy; APBI: accelerated partial breast irradiation.

Molecular subtypes	Radiosensitivity	Locoregional recurrence rate	Pattern of recurrence	Possible therapeutic approach
Luminal A	High [3,4,11,25]	Low [3,4,11,25]	True [11,26–28,30,31,33,34]	Whole breast RT To discuss: - no RT [19] - dose descalation [12] - APBI [26,34]
Luminal B	Intermediate [3,4,11,25]	Intermediate [3,4,11,25]	True and elsewhere [26–28,34,57] Regional [31,53,54]	Whole breast RT To discuss: - dose escalation [22] - regional nodal RT [16,54]
HER2/neu positive	Low [3,4,11,25]	intermediate/high (post- and pre -trastuzumab) [3,4,11,25]	True [26,34,28] Regional [11,23,31,32]	Whole breast RT To discuss: - dose escalation [23,33] - regional nodal RT [16,18,31]
Basal-like/triple negative	Very low [3,4,11,25,58]	High [3,4,11,56,58]	True [28] and elsewhere [26,27,34,58] Regional [11,23,30,31,56,58]	Whole breast RT To discuss: - regional nodal RT [16,18,29,31] - dose escalation [22,23] - radiosensitizers [25]



Grazie per l'attenzione

