III Sessione – Omissione RT mammella

Moderatori: Daniela Smaniotto,
Cynthia Aristei, Laura Lozza

12.15 Rapporteur: Carmen De Santis

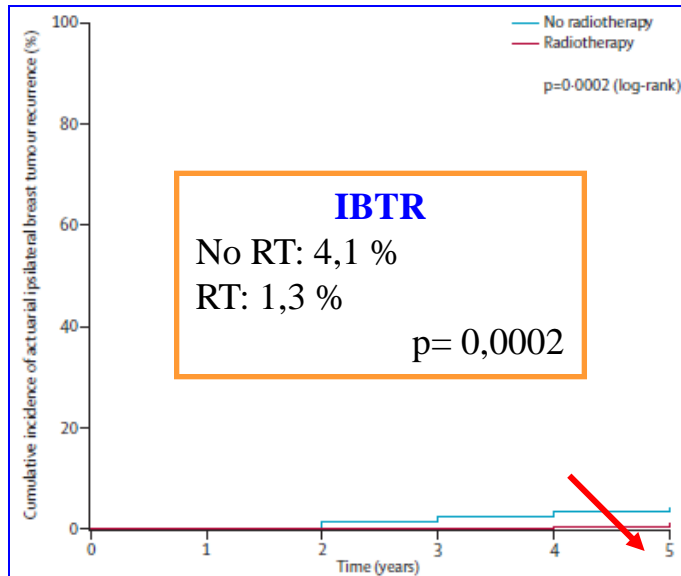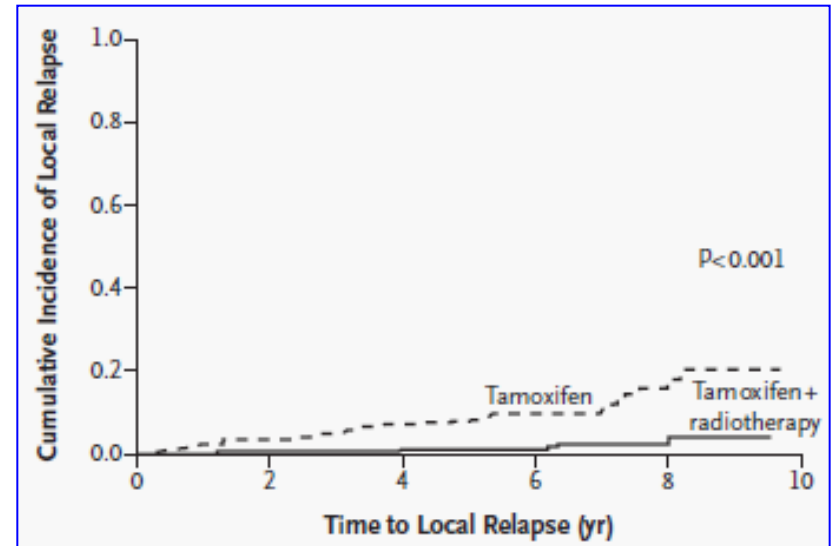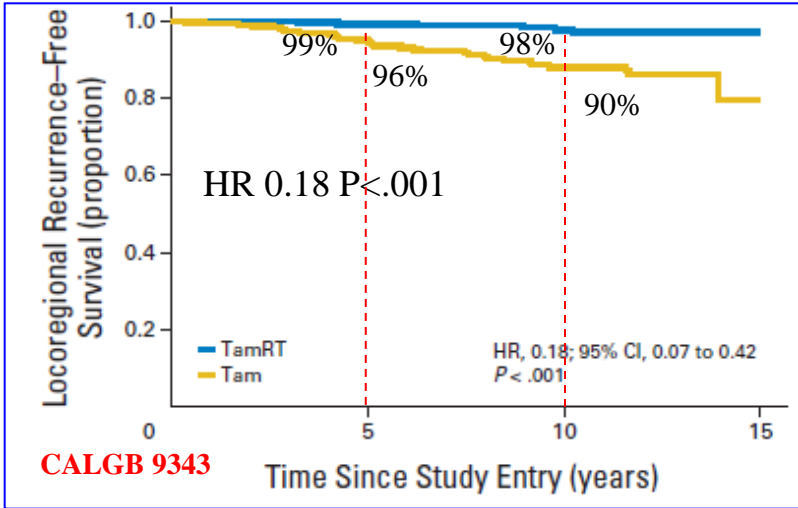12.30 Discussant: Bruno Meduri

12.45 Caso clinico: Genoveva Boboc

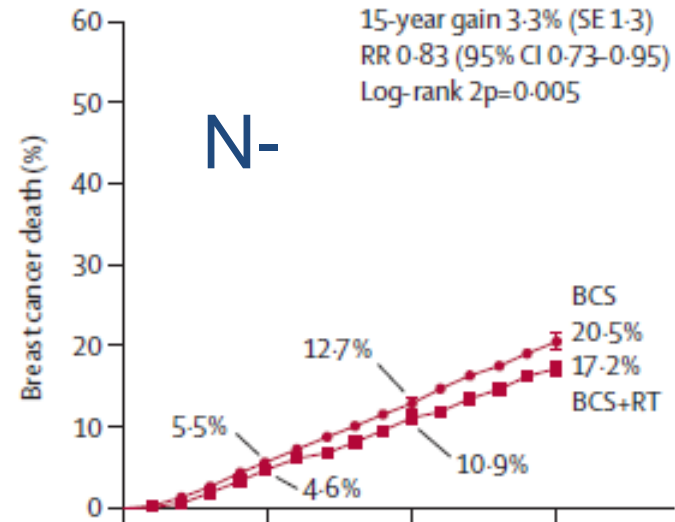# Omissione RT mammella

Bruno Meduri

A.O.U. Policlinico di Modena

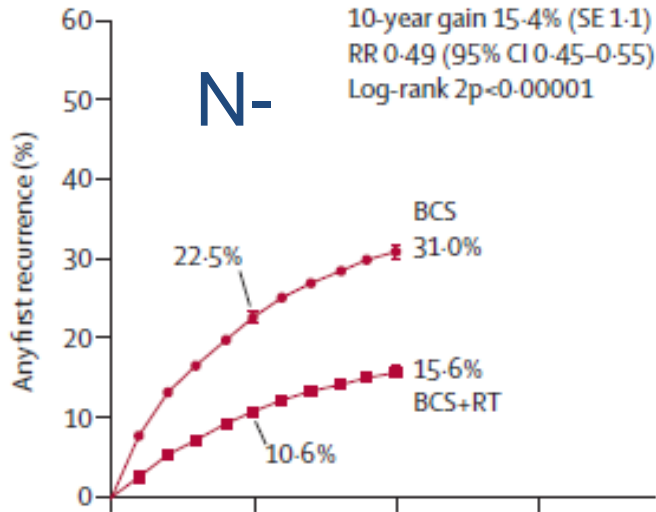SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

RT and local reccurrence

CALGB 9343

HR 0.18 P<.001

HR, 0.18; 95% CI, 0.07 to 0.42
P < .001

99% 96% 98% 90%

p<0.001

Tamoxifen

Tamoxifen+
radiotherapy

IBTR
No RT: 4,1 %
RT: 1,3 %
p= 0,0002

p=0.0002 (log-rank)

	No radiotherapy (RT)		RT	
	N events	Crude cumulative incidence (CCI) (95% confidence interval (CI))	N events	CCI (95% CI)
IBTR	40	9.2 (6.3, 12.1)	9	3.9 (1.2, 6.5)
pT1	29	8.1 (5.1, 11.0)	8	8.1 (2.3, 14.0)
pT2	11	14.6 (6.5, 22.7)	1	0.8 (0.0, 2.5)

Hughes K. S., et al. *J Clin Oncol* **2013;** 31: 2382-7   Fyles A. W., et al. *NEJM* **2004;** 351: 963-70
Kunkler I. H., et al. *Lancet Oncology* **2015;** 16: 266-73 - Martelli G., et al. *Eur J Cancer* **2015;** 51: 1358-64

RT and local reccurrence

Left graph — axis: Any first recurrence (%), values 0–60.
10-year gain 15·4% (SE 1·1)
RR 0·49 (95% CI 0·45–0·55)
Log-rank 2p<0·00001
N-
BCS 31·0%
22·5%
15·6% BCS+RT
10·6%

Right graph — axis: Breast cancer death (%), values 0–60.
15-year gain 3·3% (SE 1·3)
RR 0·83 (95% CI 0·73–0·95)
Log-rank 2p=0·005
N-
BCS 20·5%
12·7%
17·2% BCS+RT
5·5%
4·6%
10·9%

RT **halves** the rate at which the disease *recurs* and reduces the breast *cancer death* rate by **about a sixth**.

These **proportional benefits** vary little between different groups of women.

By contrast, the **absolute benefits** from radiotherapy vary substantially according to the characteristics of the patient and they can be predicted at the time when treatment decisions need to be made

Old patients ??

Age and comorbidity

Table 2. Multivariate Model of 30-Month Survival by Age, Cancer Stage, and Comorbidity

Covariate	Risk Ratio (95% Confidence Interval)
Age group, y	
55-64 (reference)	1.00
65-74	0.89 (0.61-1.28)
≥75	2.46 (1.80-3.36)
Stage	
Stage I (reference)	1.00
Stage II	2.32 (1.56-3.44)
Stage III	8.27 (5.33-12.85)
Stage IV	26.55 (17.48-40.31)
Stage unknown	3.58 (2.42-5.31)
Dichotomous variables*	
Renal failure (current/history)	3.30 (1.44-7.54)
Liver disease	2.87 (1.24-6.65)
Stroke/transient ischemic attack	2.30 (1.21-4.37)
Asthma	1.98 (1.06-3.73)
Diabetes	1.76 (1.23-2.52)
Previous malignant cancer (current/history)	1.57 (1.12-2.20)
Smoking	1.54 (1.07-2.23)
Chronic obstructive pulmonary disease	1.49 (1.01-2.17)
Hypertension	0.77 (0.60-1.00)
Arthritis	0.66 (0.48-0.91)
Lipid problems	0.23 (0.07-0.77)

1800 pts: 1017 (56%) stage I – II N0

Table 3. Cause of Death According to Age Group*

	Age, y				
	55-64	65-74	75-84	≥85	Total
Breast cancer	48 (75.0)	33 (58.9)	38 (44.7)	16 (27.6)	135 (51.3)
Other cancer	4 (6.2)	6 (10.7)	9 (10.6)	3 (5.2)	22 (8.4)
Heart disease	4 (6.2)	4 (7.1)	18 (21.2)	19 (32.8)	45 (17.1)
Cerebrovascular disease	0	1 (1.8)	4 (4.7)	8 (13.8)	13 (4.9)
Digestive system	1 (1.6)	1 (1.8)	3 (3.5)	4 (6.9)	9 (3.4)
Alzheimer disease/dementia	1 (1.6)	0	4 (4.7)	2 (3.4)	7 (2.7)
Pneumonia	0	0	2 (2.4)	3 (5.2)	5 (1.9)
COPD/other respiratory	1 (1.6)	2 (3.6)	1 (1.2)	1 (1.7)	5 (1.9)
Other	5 (7.8)	4 (7.1)	2 (2.4)	2 (3.4)	13 (4.9)
Unknown	0	5 (8.9)	4 (4.7)	0	9 (3.4)
Total No. of Deaths	64	56	85	58	263
Total No. of Patients	622	624	427	127	1800

«…Given the heterogeneity of individuals within older age groups, *age is not an appropriate criterion* for breast treatment decisions…»

Yancik R., et al. *JAMA : the journal of the American Medical Association* **2001;** 285: 885-92

Age and comorbidity

62.591 pts with early breast cancer from Danish Breast Cancer Cooperative Group Registry

	Charlson comorbidity score				Total, N
	0 N (%)	1 N (%)	2 N (%)	3+ N (%)	
Total, N	49,828	6,834	3,740	2,189	62,591
Age					
−39	2,705 (95)	82 (3)	52 (2)	21 (1)	2,860
40–49	9,283 (92)	488 (5)	208 (2)	85 (1)	10,064
50–59	13,622 (87)	1,196 (8)	600 (4)	313 (2)	15,731
60–69	12,498 (78)	1,904 (12)	1,073 (7)	572 (4)	16,047
70–79	7,885 (69)	1,839 (16)	1,062 (9)	661 (6)	11,447
80+	3,835 (60)	1,325 (21)	745 (12)	537 (8)	6,442

The proportion of pts with CCI score ≥ 1 increased significantly with age at diagnosis (P<0.0001)

	Charlson comorbidity score (%)				Total, N
	0 N (%)	1 N (%)	2 N (%)	3+ N (%)	
Total, N	49,828	6,834	3,740	2,189	62,591
Surgery					
Mastectomy	31,605 (63)	4,345 (64)	2,392 (64)	1,372 (63)	39,714
Lumpectomy	16,306 (33)	1,998 (29)	1,020 (27)	496 (22)	19,820
Biopsy alone	1,917 (4)	491 (7)	328 (9)	321 (15)	3,057

Comorbidity affected the likelihood of proper breast cancer surgery

Land L. H., et al. *Breast cancer research and treatment* **2012;** 131: 1013-20

Age and comorbidity

Cause specific cumulative incidence, % (Recurrence)

Score 0, 1, 2, 3+

10 y
22.5% for CCI 0
18.8% for CCI 1
16.0% for CCI 2
11.7% for CCI 3+

Cause specific cumulative incidence, % (Death MC, 1. event)

Score 0, 1, 2, 3+

10 y 5,4 % for CCI 0
21,7% for CCI 3+

Cause specific cumulative incidence, % (Death Other, 1. event)

Score 0, 1, 2, 3+

10 y
2,6% for CCI 0
10% for CCI 1
15,2% for CCI 2
27,9% for CCI 3+

Multivariate analysis with hazard ratio and 95% confidence intervals			
	Variable	Adjusted HR	95% CI
Breast cancer-specific mortality	CCI 0	Reference	
	CCI 1	1.30	1.24–1.36
	CCI 2	1.31	1.23–1.39
	CCI 3+	1.79	1.66–1.93
Non-breast cancer mortality	CCI 0	Reference	
	CCI 1	1.95	1.82–2.09
	CCI 2	2.14	1.97–2.33
	CCI 3+	3.56	3.22–3.93
All-cause mortality	CCI 0	Reference	
	CCI 1	1.45	1.40–1.51
	CCI 2	1.52	1.45–1.60
	CCI 3+	2.21	2.08–2.35
All P values < 0.0001			

Year of diagnosis	Charlson comorbidity score			
	0	1	2	3+
1990–1994	72.5 (71.7–73.3)	55.8 (52.8–58.6)	53.0 (48.9–56.8)	42.0 (35.8–48.1)
1995–1999	77.3 (76.6–78.1)	61.5 (58.9–63.9)	56.9 (53.5–60.3)	44.7 (39.9–49.5)
2000–2004	81.6 (80.9–82.2)	68.0 (65.9–69.9)	62.6 (59.8–65.3)	43.5 (39.8–47.0)

«…The risk of recurrence decreased with increasing CCI and CCI independent prognostic effect on SVV …pts with severe comorbidity did not benefit from the improved treatment observed for other breast cancer patients…»

Age and comorbidity

64.034 pts with breast cancer, aged ≥ 66 years (median age of 75 years)

Highest prevalence: previous cancer (16.3%), diabetes (13.0%), chronic obstructive pulmonary disease (8.8%), congestive heart failure (6.7%), stroke (4.3%)

Comorbidities	No. (%)	5-year survival rate No. (%)	95% CI	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Partially adjusted HR† (95% CI)	Fully adjusted HR‡ (95% CI)
Total patients	64034 (100)	43151 (67.4)	67.0 to 67.7	NA	NA	NA	NA
Comorbidities							
None	37306 (58.3)	27956 (74.9)	74.5 to 75.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Previous cancer	10422 (16.3)	6386 (61.3)	60.3 to 62.2	1.61 (1.56 to 1.66)§	1.48 (1.44 to 1.52)§	1.55 (1.50 to 1.60)§	1.27 (1.23 to 1.30)§
Myocardial infarction	1091 (1.7)	525 (48.1)	45.1 to 51.0	2.38 (2.21 to 2.55)§	2.14 (2.00 to 2.31)§	2.16 (2.01 to 2.32)§	1.11 (1.03 to 1.19)‖
Congestive heart failure	4280 (6.7)	1405 (32.8)	31.4 to 34.2	3.68 (3.55 to 3.82)§	2.76 (2.66 to 2.87)§	2.55 (2.46 to 2.65)§	1.70 (1.64 to 1.76)§
Peripheral vascular disease	1638 (2.6)	718 (43.8)	41.4 to 46.2	2.69 (2.54 to 2.86)§	2.16 (2.04 to 2.29)§	2.18 (2.05 to 2.31)§	1.36 (1.28 to 1.44)§
Cerebrovascular disease	2742 (4.3)	1232 (44.9)	43.1 to 46.8	2.65 (2.53 to 2.78)§	2.16 (2.06 to 2.26)§	2.08 (1.99 to 2.18)§	1.35 (1.28 to 1.42)§
COPD	5669 (8.8)	2987 (52.7)	51.4 to 54.0	2.13 (2.06 to 2.21)§	2.11 (2.04 to 2.19)§	2.14 (2.07 to 2.22)§	1.52 (1.47 to 1.58)§
Dementia	887 (1.4)	168 (18.9)	16.4 to 21.6	5.72 (5.33 to 6.14)§	3.47 (3.23 to 3.73)§	2.79 (2.59 to 3.00)§	1.96 (1.82 to 2.10)§
Paralysis	388 (0.6)	138 (35.6)	30.8 to 40.3	3.52 (3.16 to 3.93)§	2.73 (2.44 to 3.04)§	2.58 (2.31 to 2.88)§	1.23 (1.09 to 1.38)§
Diabetes	8332 (13.0)	4631 (55.6)	54.5 to 56.6	1.97 (1.91 to 2.03)§	1.97 (1.91 to 2.03)§	1.90 (1.85 to 1.96)§	1.41 (1.36 to 1.45)§
Chronic renal failure	590 (0.9)	139 (23.6)	20.2 to 27.1	4.90 (4.49 to 5.35)§	4.52 (4.14 to 4.94)§	4.42 (4.04 to 4.83)§	2.20 (2.02 to 2.41)§
Liver disease	186 (0.3)	59 (31.7)	25.2 to 38.5	3.46 (2.94 to 4.06)§	3.78 (3.22 to 4.44)§	4.04 (3.44 to 4.76)§	2.32 (1.97 to 2.73)§
Stomach ulcer	705 (1.1)	387 (54.9)	51.1 to 58.5	1.91 (1.74 to 2.10)§	1.73 (1.57 to 1.89)§	1.71 (1.56 to 1.88)§	1.12 (1.02 to 1.23)#
Rheumatoid arthritis	1246 (2.0)	747 (60.0)	57.2 to 62.6	1.70 (1.58 to 1.83)§	1.65 (1.53 to 1.78)§	1.71 (1.58 to 1.84)§	1.27 (1.18 to 1.37)§
Charlson comorbidity index score							
0	37306 (58.3)	27956 (74.9)	74.5 to 75.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	NA
1	17946 (28.0)	11392 (63.5)	62.8 to 64.2	1.54 (1.50 to 1.57)§	1.45 (1.41 to 1.48)§	1.45 (1.41 to 1.48)§	NA
2	5639 (8.8)	2787 (49.4)	48.1 to 50.7	2.34 (2.25 to 2.42)§	2.13 (2.06 to 2.21)§	2.12 (2.05 to 2.20)§	NA
≥3	3143 (4.9)	1016 (32.3)	30.7 to 34.0	3.69 (3.54 to 3.84)§	3.24 (3.11 to 3.38)§	3.19 (3.06 to 3.32)§	NA

Patnaik J. L., et al. *J Natl Cancer Inst* **2011;** 103: 1101-11

Age and comorbidity
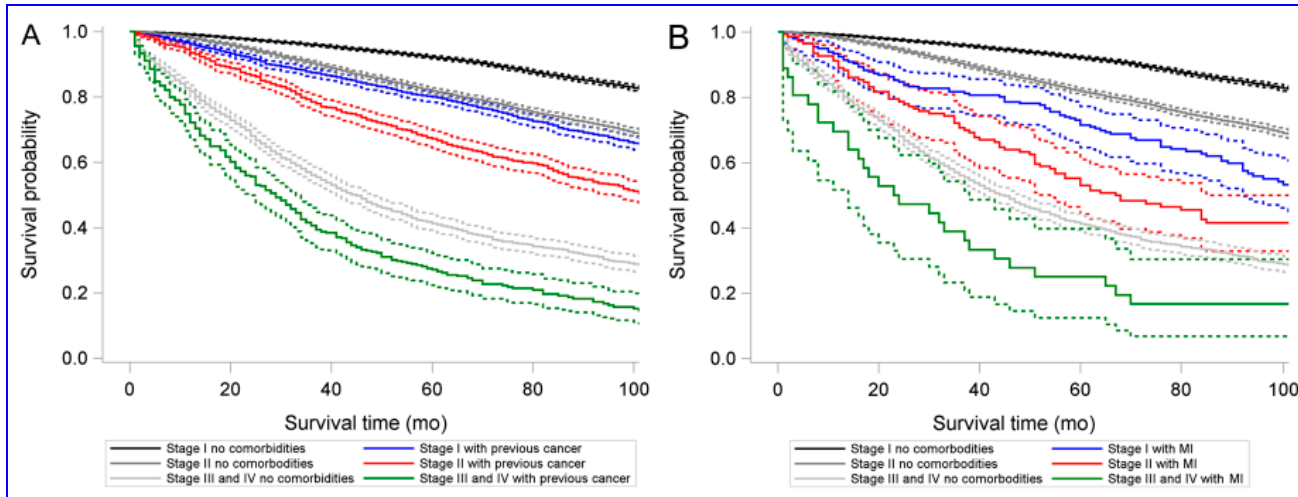
Patients aged > 65 years with stage I tumors with comorbidities had svv curves similar to patients with stage II tumors who had no comorbidities

Patnaik J. L., et al. *J Natl Cancer Inst* **2011;** 103: 1101-11
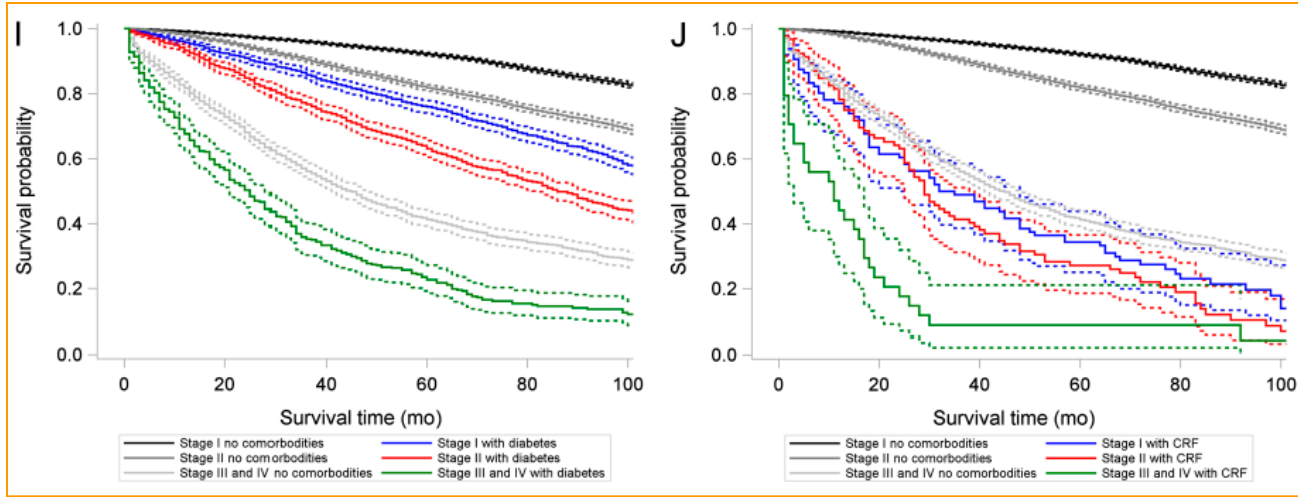
Endocrine therapy

Endocrine therapy discontinuation

961 pts, > 65 years old diagnosed with stage I to IIB ER-positive

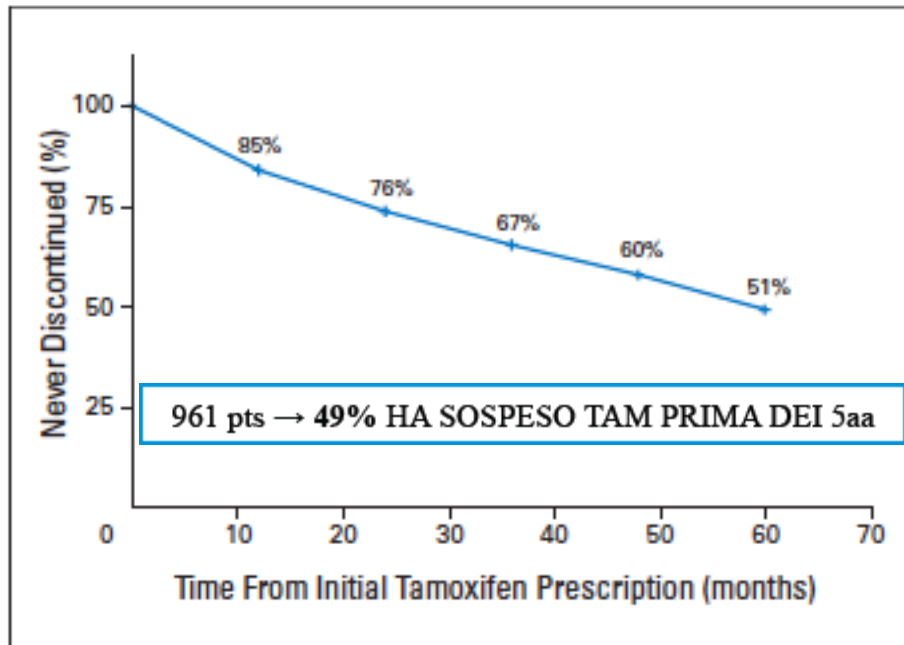**Fig 2.** Proportion of older women with breast cancer who never discontinued tamoxifen over a 5-year follow-up period (life-table analysis).

Early discontinuers were more likely than late discontinuers as a result of adverse effects (43% *v* 24%, respectively; *P*=.0001

The rate of tam discontinuation was 15% in the first year and remained fairly constant at less than 10% in each of the succeeding 4 years

Owusu C., et al. *J Clin Oncol* **2008;** 26: 549-55
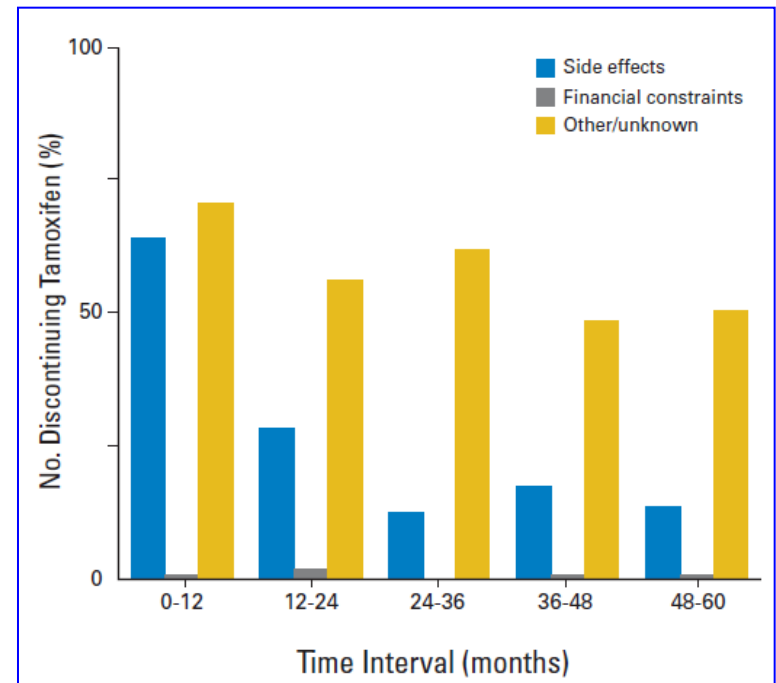
Endocrine therapy discontinuation

Predictors of tamoxifen discontinuance

Characteristic	Never Discontinued No. of Patients (n = 519)	%	Ever Discontinued No. of Patients (n = 442)	%	Univariate Hazard Ratio	95% CI	Multivariate Hazard Ratio	95% CI
Age, years								
65-69	213	63	127	37	1.00		1.00	
70-74	163	55	132	45	1.26	0.99 to 1.60	1.25	0.98 to 1.60
75-79	81	51	77	49	1.46*	1.10 to 1.93*	1.41*	1.06 to 1.87*
≥ 80	62	40	106	63	2.28*	1.76 to 3.00*	2.02*	1.53 to 2.66*
Race/ethnicity								
White, non-Hispanic	409	52	372	47	1.00			
White, Hispanic	40	67	20	33	0.60*	0.39 to 0.95*	—†	—
African American	48	57	36	43	0.85	0.60 to 1.20	—	—
Other	22	61	14	39	0.74	0.43 to 1.26	—	—
Charlson Comorbidity Index								
0	389	57	291	43	1.00			
1	116	48	128	52	1.30*	1.06 to 1.60*	—	—
≥ 2	14	38	23	62	1.56*	1.02 to 2.39*	—	—
Tumor size, cm								
≤ 1	120	54	104	46	1.00			
> 1 to ≤ 2	246	56	193	44	0.92	0.72 to 1.16	—	—
> 2	153	51	145	49	1.03	0.80 to 1.33	—	—
Lymph node involvement								
Positive	191 (57)	14243			1.00			
Negative/not assessed	323	52	293	47	1.22*	1.00 to 1.50*	—	—
Histologic grade								
Well differentiated	92	56	72	44	1.00			
Mod differentiated	213	58	154	42	0.95	0.72 to 1.25	—	—
Poorly differentiated	95	44	120	56	1.35	1.00 to 1.80	—	—
Not assessed	119	55	96	45	1.02	0.75 to 1.38	—	—
Estrogen receptor status								
Positive	486	55	396	45	1.00		1.00	
Indeterminant	33	42	46	58	1.54*	1.14 to 2.09*	1.36*	1.00 to 1.85*
Progesterone receptor status								
Positive	377	56	299	44	1.00			
Negative	96	52	87	48	1.11	0.88 to 1.41	—	—
Indeterminant	46	45	56	55	1.42*	1.07 to 1.89*	—	—
Primary therapy								
Mastectomy	299	56	229	43	1.00		1.00	
BCS with radiotherapy	195	55	159	45	1.11	0.90 to 1.35	1.14	0.93 to 1.40
BCS without radiotherapy	25	32	54	68	2.12*	1.58 to 2.85*	1.62*	1.18 to 2.22*
Chemotherapy								
Yes	44	63	28	37	1.00			
No	475	53	416	47	1.32	0.89 to 1.96	—	—

On multivariable analysis, **discontinuers** were more likely:
- to be *aged > 70 years*
- have received *BCS without radiotherapy*

Molecular Subtypes

Molecular subtypes

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. Nielsen, Sharon Nofech-Mozes, Martin C. Chang, Timothy J. Whelan, Lorna M. Weir, Ivo A. Olivotto, David R. McCready, and Anthony W. Fyles

"…the **primary objective** was to define intrinsic subtyping as a
predictive biomarker of RT benefit …"

A — Luminal A — 3.3 % vs 7.3 %
B — Luminal B — 7.8 % vs 13.3 %
C — HER2-enriched basal-like — 6 % vs 37.9 %
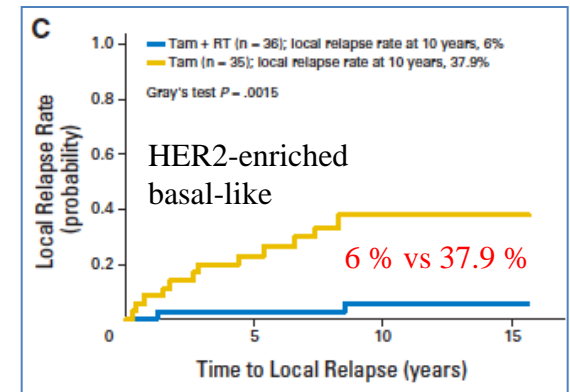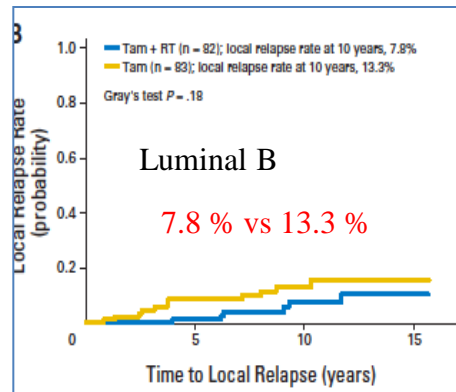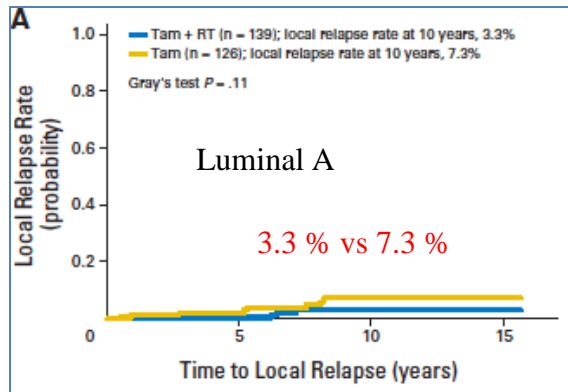
"In conclusion, a six-IHC-biomarker panel was *prognostic for IBR* but
not predictive of benefit from RT …"

Liu F. F., et al. *J Clin Oncol* **2015;** 33: 2035-40

Conclusions 1

Age is not an appropriate criterion

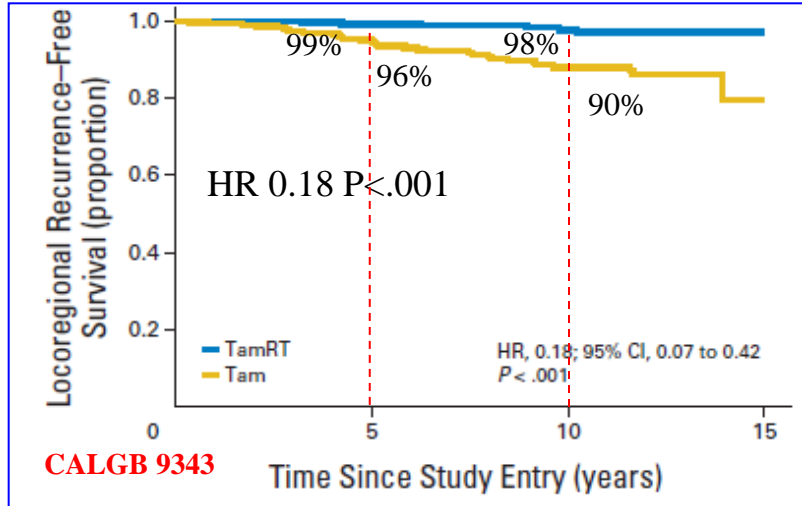*Comorbidities*: independent prognostic effect on SVV

Endocrine therapy discontinuers were more likely to be *aged > 70 years and/or* have received *BCS without radiotherapy*

Biomarker panel was *prognostic for IBR*

Very low risk patients: early-stage G1-2 luminal A with comorbidities
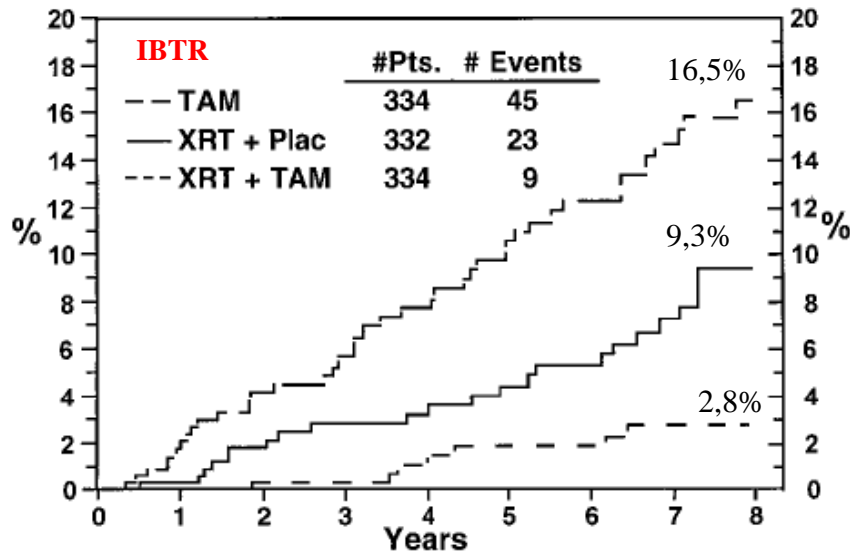**Treatment omission**

Local reccurrence

CALGB 9343

HR 0.18 P<.001

HR, 0.18; 95% CI, 0.07 to 0.42
P < .001

- TamRT
- Tam

99% 96% 98% 90%

IBTR

	#Pts.	# Events
TAM	334	45
XRT + Plac	332	23
XRT + TAM	334	9

16,5% 9,3% 2,8%

"…A healthy 70-year-old woman has a high chance of living more than 10 years, risking a one-in-10 rate of local recurrence if RT is omitted and a one-in-50 rate if radiotherapy is given.

Conversely, in patients with significant comorbidities, the benefit of endocrine therapy can be questioned: the survival benefit of systemic treatment in patients with so-called low-risk tumors is mainly seen after 5 years, whereas the benefit of radiotherapy in reducing local recurrence is considerable in the first 5 years…"

Fisher B. *Journal of Clinical Oncology* **2002;** 20: 4141 - Kaidar-Person O., et al. *J Clin Oncol* **2013;** 31: 4569

Adverse effect

"…**Radiation** treatments are well tolerated and, when delivered using modern technologies, carry a low risk of serious morbidity…"

Smith B. D., et al. *J Clin Oncol* **2013;** 31: 2367-8
Williams L. J., et al. *Health technology assessment* **2011;** 15: i-xi, 1-57

Endocrine therapy:
- Tamoxifen:
  - *Thromboembolic* events significantly increased (tamoxifen vs placebo 43% vs 17% ($p = 0.001$)). There was also a significant excess of deaths from all causes in the tamoxifen treated group
  - *Endometrial cancer*

Cuzick J., et al. *Lancet* **2002;** 360: 817-24
Fisher B., et al. *J Natl Cancer Inst* **1994;** 86: 527-37

- Aromatase inhibitors:
  - *Arthralgia* (an important cause of treatment discontinuation),
  - *Reduced bone mineral density* and increased *fracture risk* (mortality of up to 20% at 6 months in older patients)

Howell A., et al. *Lancet* **2005;** 365: 60-2
Forbes J. F., et al. *Lancet Oncol* **2008;** 9: 45-53
Curry L. C., et al. *Journal of advanced nursing* **2003;** 42: 347-54

Cost-effectiveness

Most studies report only direct medical costs …
…management of the *side effects* or complications, identification and management of *recurrences* (if a treatment is to be omitted) *must be included* in the overall costs

In PRIME trial, medical costs of the <u>addition of WBI</u> were of the order of *£2000* per pt

Prescott R. J., et al. *Health technology assessment* **2007;** 11: 1-149

Hypofractionated regimens (15 or 16 fractions) or APBI → lower costs

Cost for <u>treatment of local recurrence</u> is estimated at *$20,879*

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

Cost-Benefit Analysis of Post-Lumpectomy Treatment in Elderly Women.

J. Nangia[1], S. Chen[2], R. Rao[1], and K. Griem[2]

32nd annual San Antonio Breast Cancer Symposium

«…tamoxifen alone would be the treatment of choice if considering total cost alone, but when including side effects and deaths related to this treatment, then the overall cost of *tamoxifen would be much higher than WBI*..»

Conclusions

Very low risk patients: early-stage G1-2 luminal A with comorbidities

~~Omission RT~~

Omissione OT

…tutti gli altri raggiungono una vetta cercando da qualche parte un sentiero sulla montagna. Nash scalerebbe un´altra montagna e da quella vetta lontana illuminerebbe con un riflettore la prima vetta…