



Associazione  
Italiana  
Radioterapia  
Oncologica

# V ZOOM Journal Club 2015

Bologna, 19 Febbraio 2016

NH Hotel De La Gare

**Coordinatore** Alfio Di Grazia

**Comitato esecutivo:** Fiorenza De Rose, Maria Carmen De Santis,  
Lorenza, Marino, Icro Meattini, Bruno Meduri, Isabella Palumbo



## 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 della Radioterapia

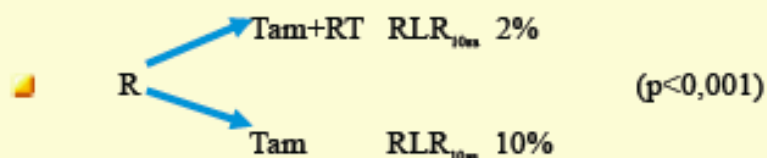
## Perchè?

1. Impegno giornaliero per un arco temporale anche di molte settimane
2. Accessibilità limitata ai centri di radioterapia
3. Influenza positiva sul carico di lavoro nelle strutture di RT
4. Diminuizione costi SSN e personali
5. Diminuzione del rischio di effetti collaterali legati al trattamento radiante e di aggravare patologie preesistenti
6. Invecchiamento della popolazione → **AUMENTO INCIDENZA Ca mammario CON ETA' !**

## Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343

Kevin S. Hughes, Lauren A. Schnaper, Jennifer R. Bellon, Constance T. Cirrincione, Donald A. Berry, Beryl McCormick, Hyman B. Muss, Barbara L. Smith, Clifford A. Hudis, Eric P. Winer, and William C. Wood

636 PTS,  $\geq 70$  anni, cT1, cN0- ER+, **aggiornamento a 12,6 anni FU**



- CONFERMATO IL VANTAGGIO IN TERMINI DI RIDUZIONE DI RL
- NON VANTAGGIO IN OS, S ca specifica, DDFS, O PRESERVAZIONE MAMMARIA
- GLOBALMENTE SOLO IL 3 % PTS DECEDUTA PER CA MAMMARIO
- NELLE PTS BASSO RISCHIO, LE CAUSE PRINCIPALI DI MORTE SONO DA ATTRIBUIRE A PATOLOGIE DIVERSE

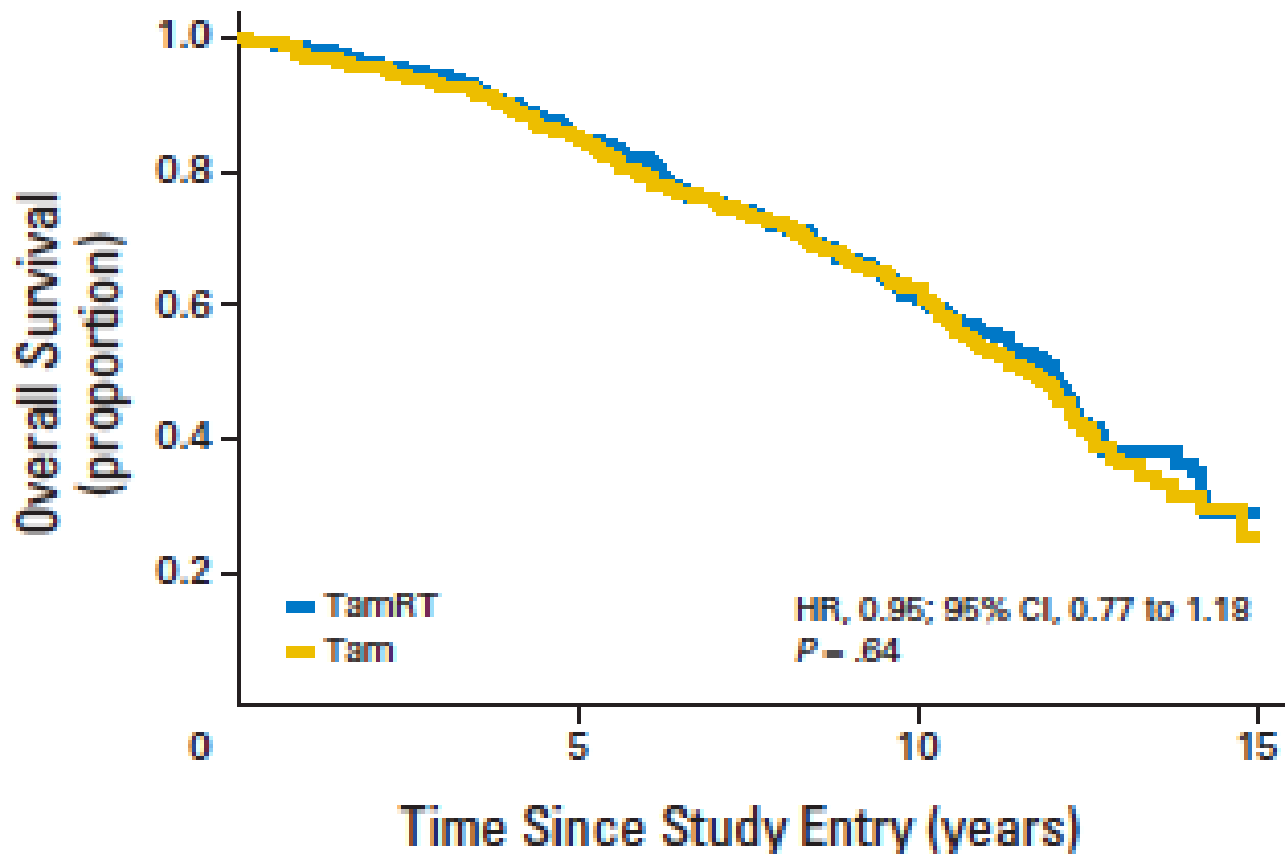
**TAM DA SOLO  
OPZIONE RAGIONEVOLE  
PER DONNE >70 , ER+ IN STADIO PRECOCE DI  
MALATTIA**

**Hughes KS JCO 2013;31:2382-2387**

Locoregional Recurrence-Free Survival (proportion)

No. at risk  
TamRT  
Tam

Fig 2. Tir  
alone; Tam



No. at risk

TamRT	317	264	168	7
Tam	319	262	167	4

CI, 0.17 to 1.48

15

rs)

7

2

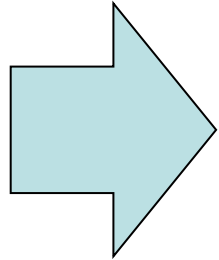
; Tam, tamoxifen

Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.



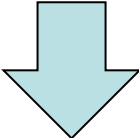
# Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators



1326 pts (76 centri) 2003-2009  
>65 aa (Età mediana 70 aa)  
T1-T2 < 3 cm pN0  
Rec pos in OT  
Margini > 1mm  
LVSI + o G3  
Nessuna informazione su Her2neu, PS e comorbidity

Endpoint primario  
Incidenza di recidiva locale



R	NO RT	→	IBTR 4,1 %
	RT	→	IBTR 1,3 %

P= 0,0002

Dosi RT 40-50 Gy in 15-25 frazioni  
Boost (16% pts) e 10-15 Gy o  
impianto di iridio 20 Gy  
all'isodose dell'85%

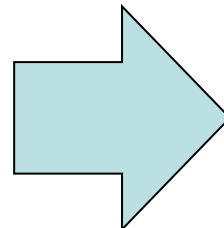


# Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

*Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators*

- FU mediano 5 aa
- Differenza statisticamente significativa in IBTR con un HR= 5.19 (95%CI 1.99-13.52; **p=0.0007**) e con una riduzione del rischio di recidiva a 5 anni del 2.9%
- =OS (93.9% a 5 aa); RLR; Tumori mammari controlaterali e Metastasi a distanza
- Unico fattore predittivo di recidiva locale è l'omissione della radioterapia con un HR 4.87 (95%CI 1.86-12.74; **p=0.0013**) sebbene la bassa espressione recettoriale (120 pts 9%) e il grado 3 (36 pts 3%) sono al limite della significatività (**p=0.06**)
- La >>> parte delle morti non sono CA correlate per entrambi i bracci

**ANALISI NON PIANIFICATA**



Il tasso di recidiva locale nei pz con bassa espressione di ER (9%) è 10.3 % vs 0% (**p= 0.026**)



Available at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)



## Omission of radiotherapy in elderly patients with early breast cancer: 15-Year results of a prospective non-randomised trial



Gabriele Martelli <sup>a,\*</sup>, Patrizia Boracchi <sup>b</sup>, Eleonora Guzzetti <sup>a</sup>, Giuseppe Marano <sup>b</sup>,  
Laura Lozza <sup>c</sup>, Roberto Agresti <sup>a</sup>, Cristina Ferraris <sup>a</sup>, Domenico Piromalli <sup>a</sup>,  
Marco Greco <sup>a</sup>

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Available online 20 May 2015

Table 1

Characteristics of 627 consecutive elderly ( $\geq 70$  years) early, cN0 breast cancer patients, according to whether or not they received radiotherapy (RT).

	No radiotherapy (RT) ( <i>N</i> 420)	RT ( <i>N</i> 207)	Overall ( <i>N</i> 627)
Median age in years (range)	76 (70–91)	75 (70–88)	76 (70–91)
Axillary surgery, <i>N</i> (%)			
No	333 (79.3%)	127 (61.4%)	460 (73.4%)
Yes	87 (20.7%)	80 (38.6%)	167 (26.6%)
Tumour size, <i>N</i> (%)			
pT1	344 (81.9%)	86 (41.5%)	430 (68.6%)
pT2	76 (18.1%)	121 (58.5%)	197 (31.4%)
Oestrogen receptor (ER), <i>N</i> (%)			
ER-positive	373 (88.8%)	169 (81.6%)	542 (86.4%)
ER-negative	31 (7.4%)	27 (13.0%)	58 (9.3%)
Not assessed	16 (3.8%)	11 (5.3%)	27 (4.3%)
Progesterone receptor (PGR), <i>N</i> (%)			
PgR-positive	265 (63.1%)	116 (56.0%)	381 (60.8%)
PgR-negative	139 (33.1%)	80 (38.6%)	219 (34.9%)
Not assessed	16 (3.8%)	11 (5.3%)	27 (4.3%)
Histology, <i>N</i> (%)			
Invasive ductal carcinoma	276 (65.7%)	137 (66.2%)	413 (65.9%)
Invasive lobular carcinoma	90 (21.4%)	51 (24.6%)	141 (22.5%)
Other invasive carcinoma	54 (12.9%)	19 (9.2%)	73 (11.6%)





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### pT1 patients

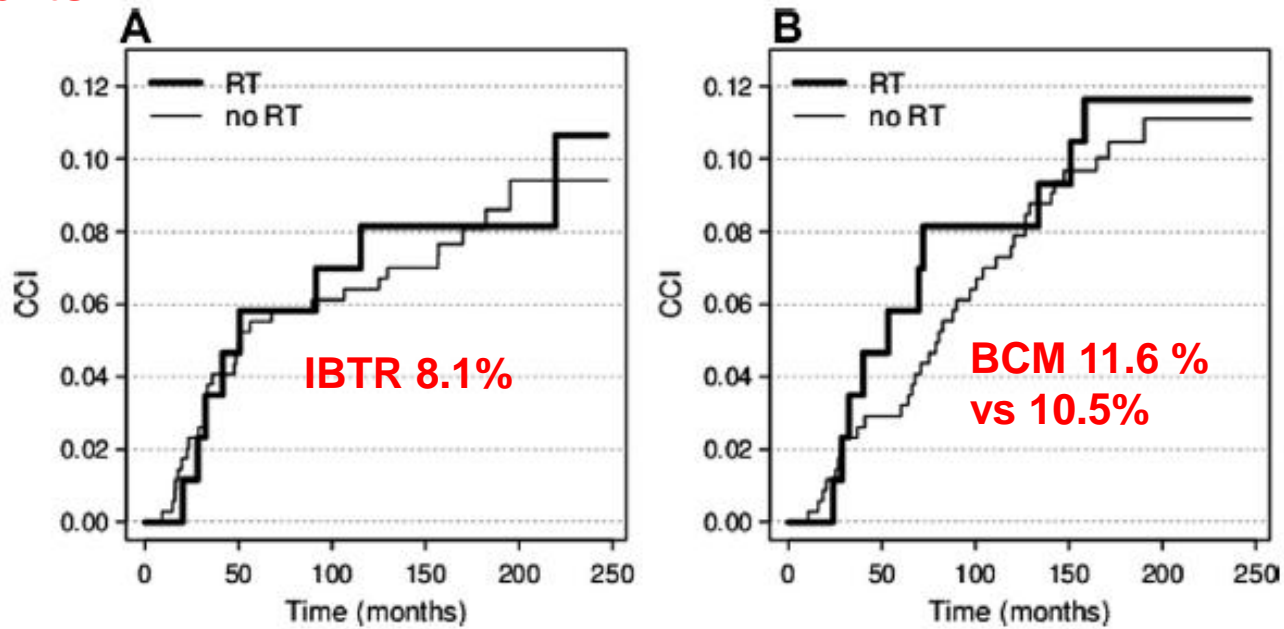


Fig. 1. Estimated crude cumulative incidences (CCIs) of ipsilateral breast tumour recurrence (IBTR) (A) and breast cancer mortality (B) in pT1 patients. Thin line: no radiotherapy (RT); thick line: RT.



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## pT2 patients

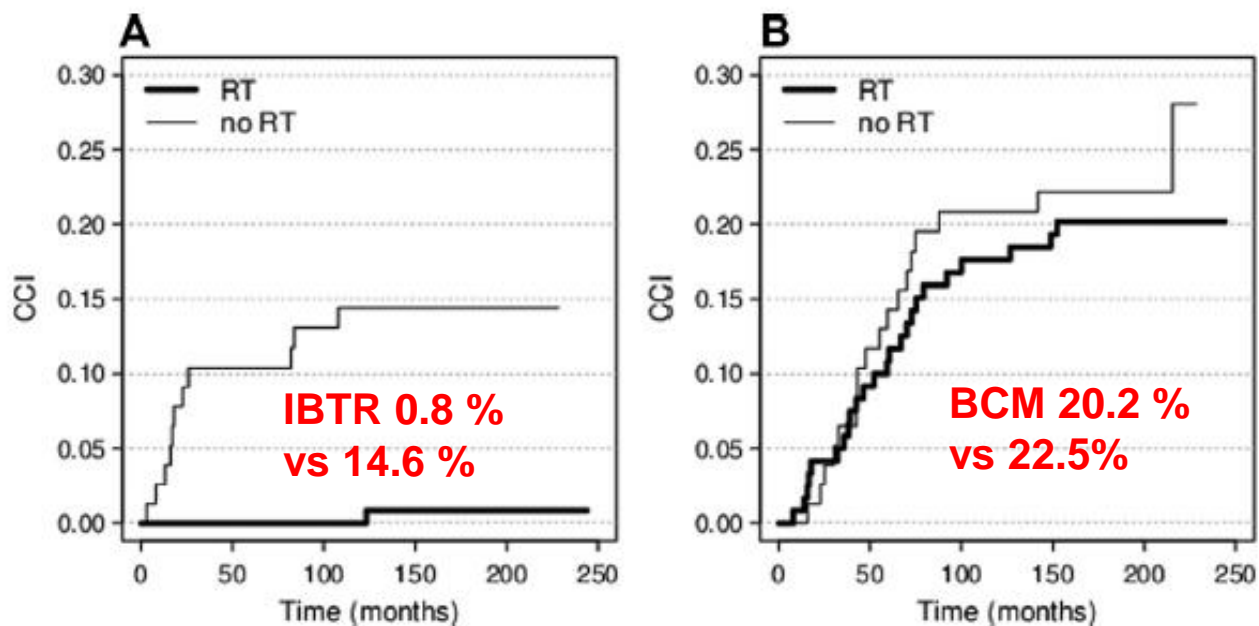


Fig. 2. Estimated crude cumulative incidences (CCIs) of ipsilateral breast tumour recurrence (IBTR) (A) and breast cancer mortality (B) in pT2 patients. Thin line: no radiotherapy (RT); thick line: RT.

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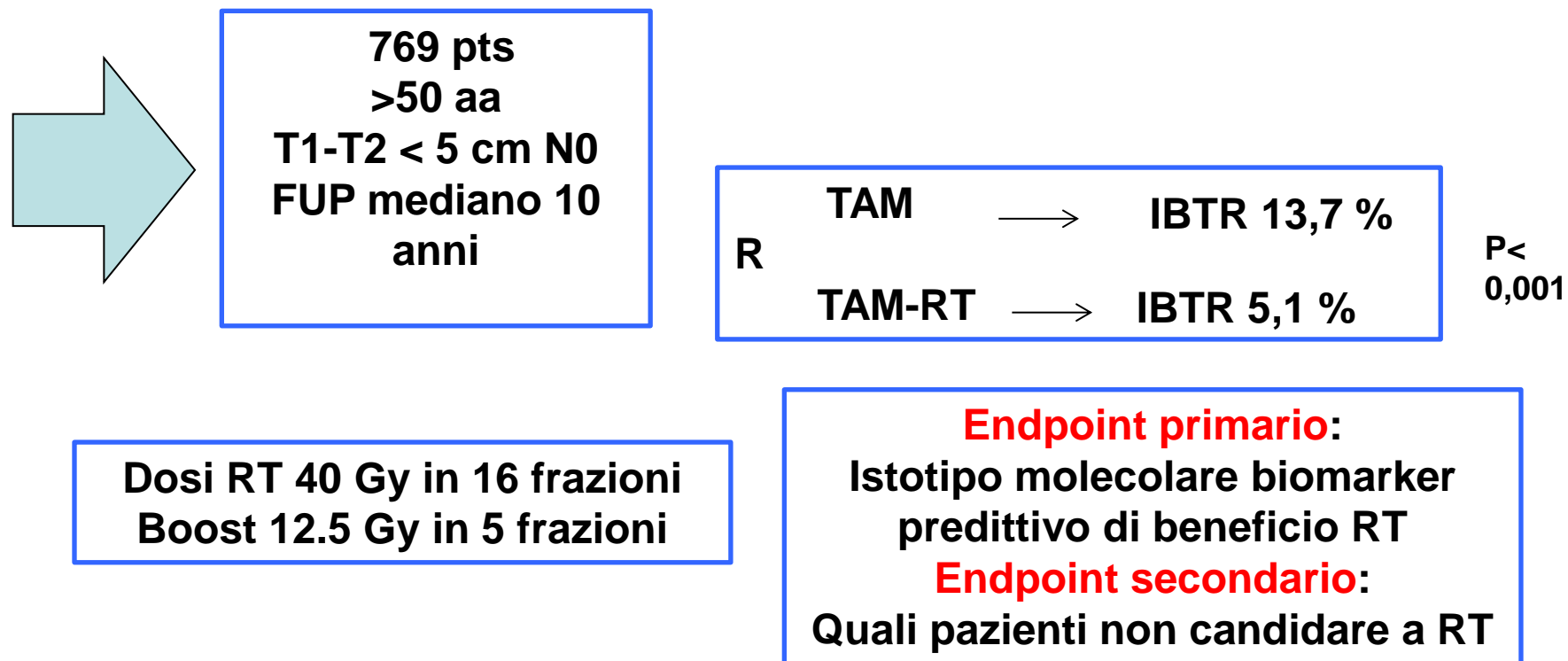
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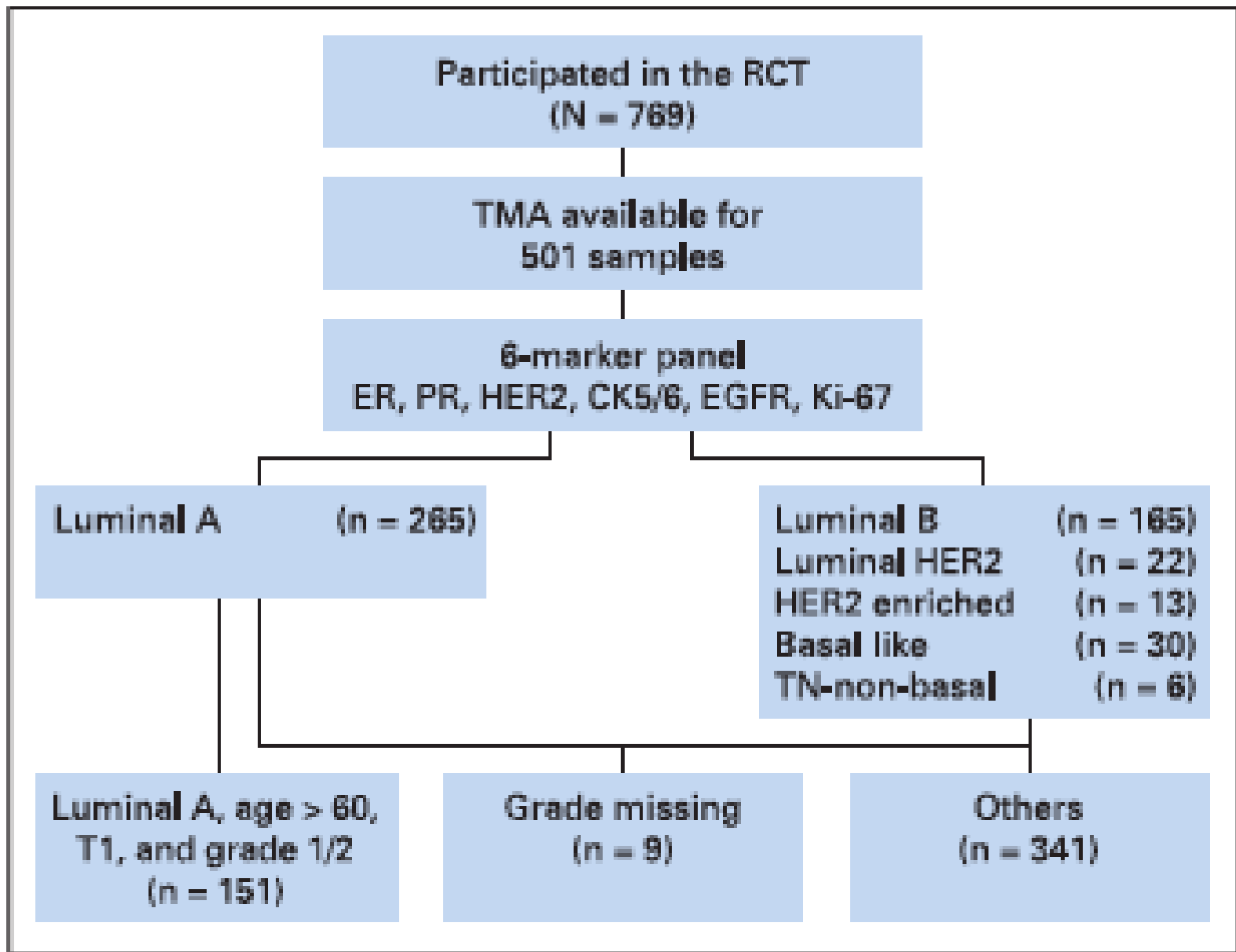
	Hazard ratio (HR) (95% confidence interval (CI))	<i>P</i> value
<b>Ipsilateral breast tumour recurrence (IBTR)</b>		
Radiotherapy (RT) versus no RT		
pT1	0.90 (0.41, 2.02)	0.806
pT2	0.05 (0.01, 0.39)	0.004
For 10% increase in propensity score	1.19 (0.71, 1.47)	0.806
<b>Distant metastasis</b>		
RT versus No RT		
pT2 versus pT1	0.94 (0.54, 1.62)	0.814
For 10% increase in propensity score	2.63 (1.52, 4.55)	<0.001
	1.35 (1.13, 1.63)	0.001
<b>Breast cancer mortality</b>		
RT versus No RT		
pT2 versus pT1	0.85 (0.53, 1.36)	0.498
For 10% increase in propensity score	2.43 (1.52, 3.89)	0.001
	1.24 (1.06, 1.45)	0.008

- RT ha un effetto protettivo sulla recidiva locale nei pts pT2 (**p 0.04**) ma non nei pT1 (**p 0.806**).
- Gli effetti della RT sulle metastasi a distanza e sulla mortalità cancro-correlata è indipendente dal pT (**p=0.806** per i pT1 e **0.784** per i pT2)
- Nessuna analisi dell'effetto dell'ER status sull' IBTR per la presenza di pochi eventi e pochi pts con recettori negativi (54 pts)

## 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. Olivetto, David R. McCready, and Anthony W. Fyles





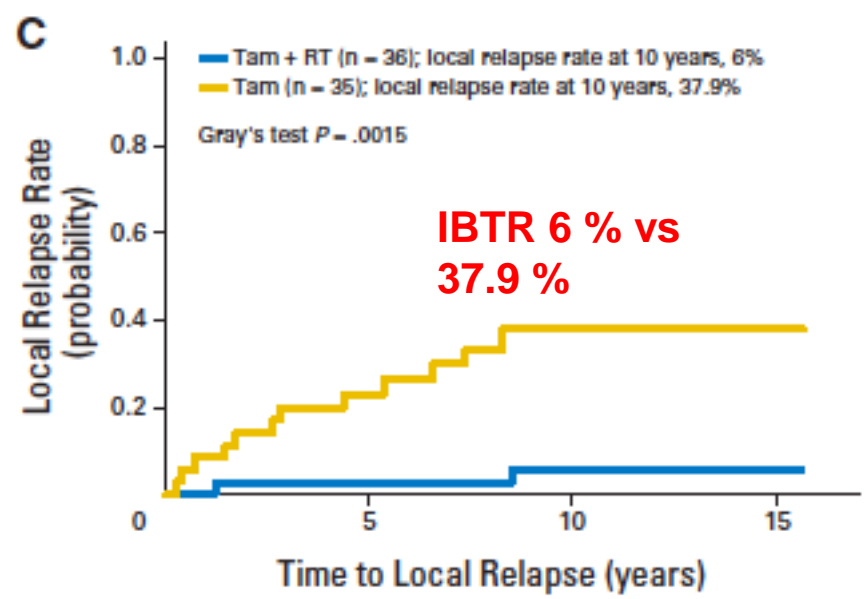
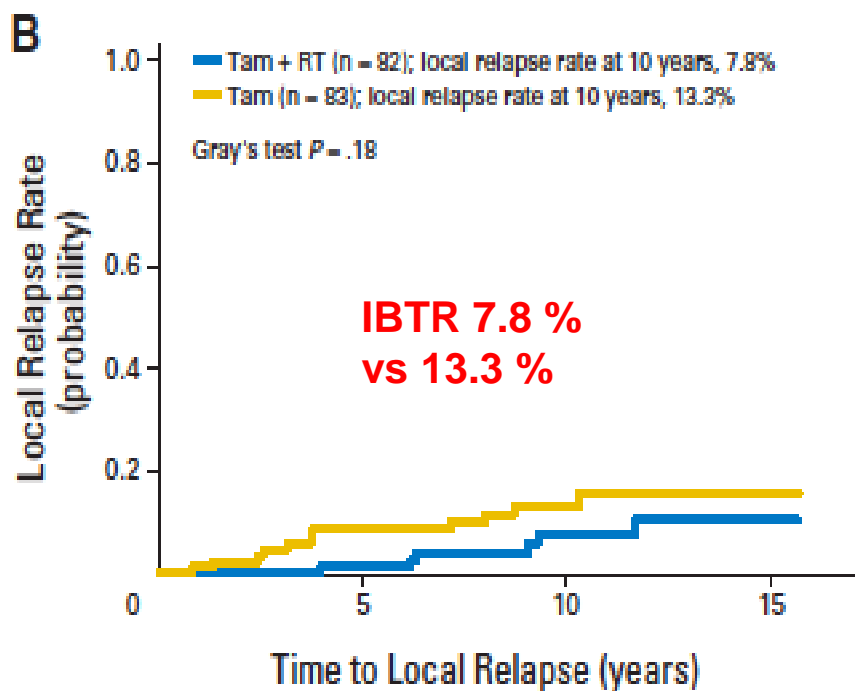
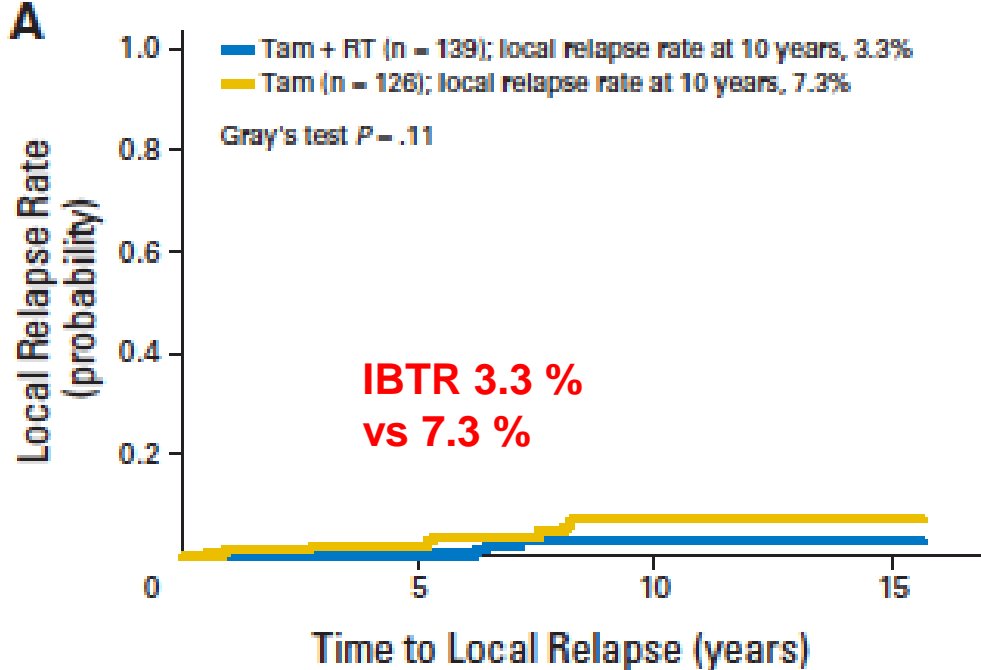
**Table 2. Univariable Analysis of the Stratified Trial Biomarkers (T stage, age) Assessed With Histologic Grade, Treatment Arm, and Intrinsic Subtype**

Variable	No.	IBR at 10 Years (%)	P
<b>Age, years</b>			
≤ 60	130	14.1	.068
> 60	371	7.4	
<b>T category*</b>			
T1	412	8.4	.15
T2	87	13.5	
<b>Grade†</b>			
1 to 2	365	6.8	.015
3	109	14.3	
<b>Treatment</b>			
Tamoxifen + RT	257	5.1	< .001
Tamoxifen	244	13.7	
<b>Subtype</b>			
Luminal A	265	5.2	< .001
Luminal B	165	10.5	
Other	71	21.3	

**Table 3.** Multivariable Analysis of IBR for the Stratified Trial Biomarkers, Grade, Treatment, and Intrinsic Subtype (significant variables shown)

Covariate	HR	95% CI	P
Tamoxifen + RT v tamoxifen	0.32	0.16 to 0.62	< .001
<b>Subtype</b>			
Luminal A v high risk	0.21	0.1 to 0.46	< .001
Luminal B v high risk	0.45	0.22 to 0.92	.028
Luminal A v luminal B	0.48	0.23 to 0.98	.045
Overall			< .001

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



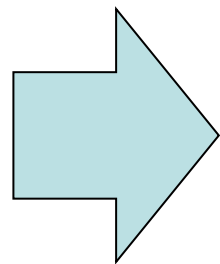


*...Dopo la pubblicazione dello studio  
CALGB 9343 di quanto è diminuito l'utilizzo  
della radioterapia in questo setting di  
pazienti?*

# The Use of Adjuvant Radiotherapy in Elderly Patients With Early-Stage Breast Cancer: Changes in Practice Patterns After Publication of Cancer and Leukemia Group B 9343

Manisha Palta, MD<sup>1</sup>; Priya Palta, PhD<sup>2</sup>; Nrupen A. Bhavsar, PhD<sup>3</sup>; Janet K. Horton, MD<sup>1</sup>; and Rachel C. Blitzblau, MD,PhD<sup>1</sup>

**Studio retrospettivo di popolazione basato sui dati del SEER (20 registri tumori) che confronta l'utilizzo della RT prima e dopo il 2004**



**40,583 pts  
70-85 aa  
T1 < 2 cm N0  
Rec pos (80% ER e  
PR positive)  
<15% G3**

**Endpoint primario: Radiotherapy Delivery in 2 time cohorts**



**2000-2004**



**2005-2009**

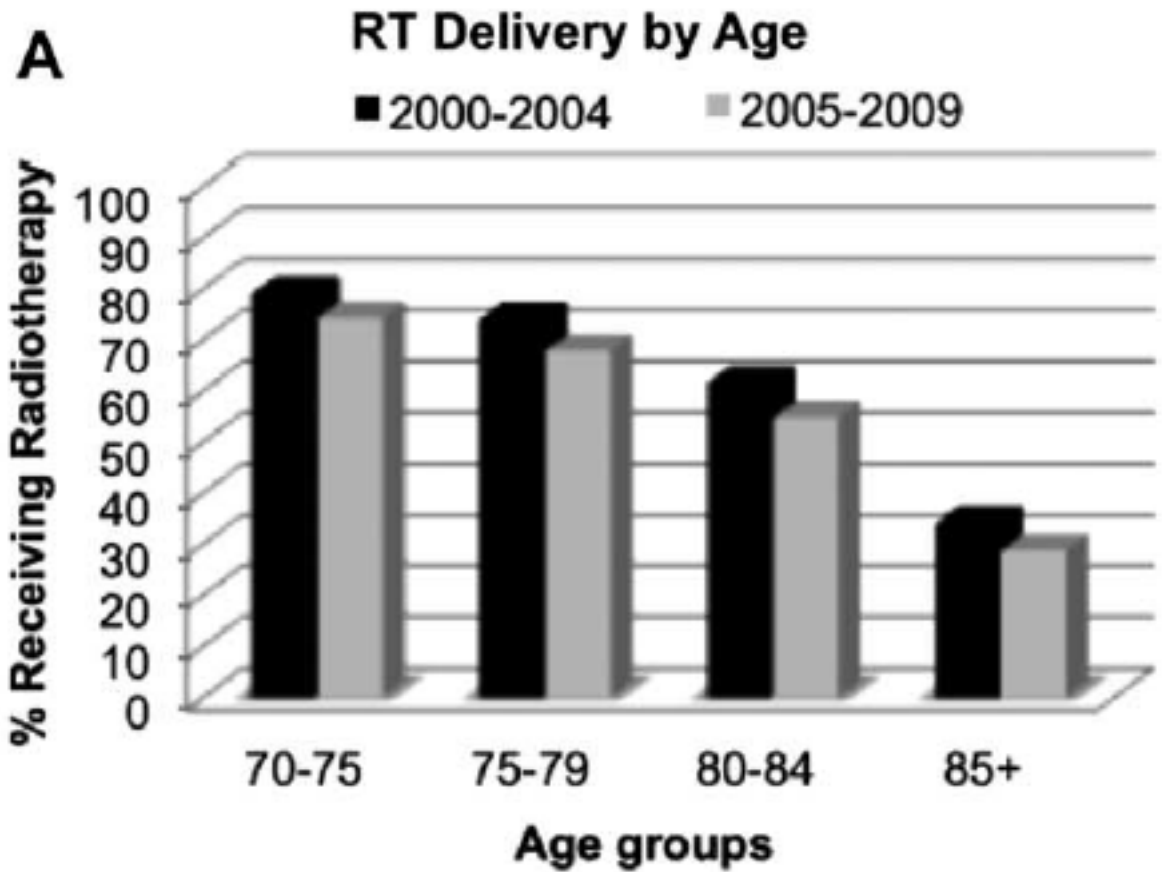
**TABLE 2.** Radiotherapy Delivery and Type of Delivery by Cohort: SEER Study, 2000 to 2009 (N=40,583)

	SEER Time Cohort	
	2000-2004 n = 18,795	2005-2009 n = 21,788
Radiotherapy delivered, no. (%)		
Yes	12,881 (68.6)	13,440 (61.7)
No	5476 (29.1)	7883 (36.2)
Unknown	438 (2.3)	465 (2.1)
Type of radiotherapy delivered, no. (%)		
Beam radiation	12,411 (66.0)	11,811 (54.2)
Combination, beam isotope	91 (0.5)	55 (0.2)
Implant	265 (1.4)	1342 (6.2)
Isotope	11 (0.06)	15 (0.1)
Radiation, NOS	103 (0.5)	217 (1.0)
None	5125 (27.3)	7290 (33.5)
Refused	351 (1.9)	593 (2.7)
Recommended, unknown if administered	315 (1.7)	370 (1.7)
Unknown	123 (0.6)	95 (0.4)

Abbreviations: NOS, not otherwise specified; SEER, Surveillance Epidemiology and End Results.

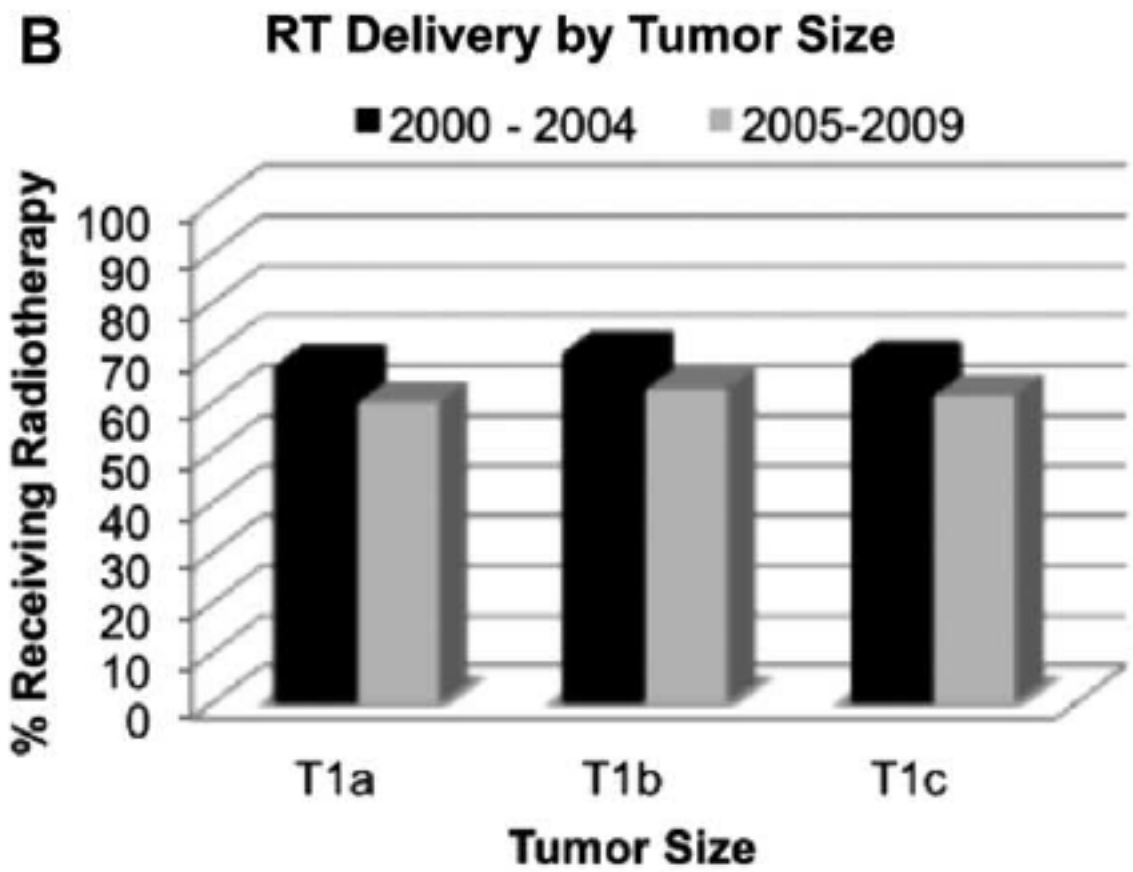
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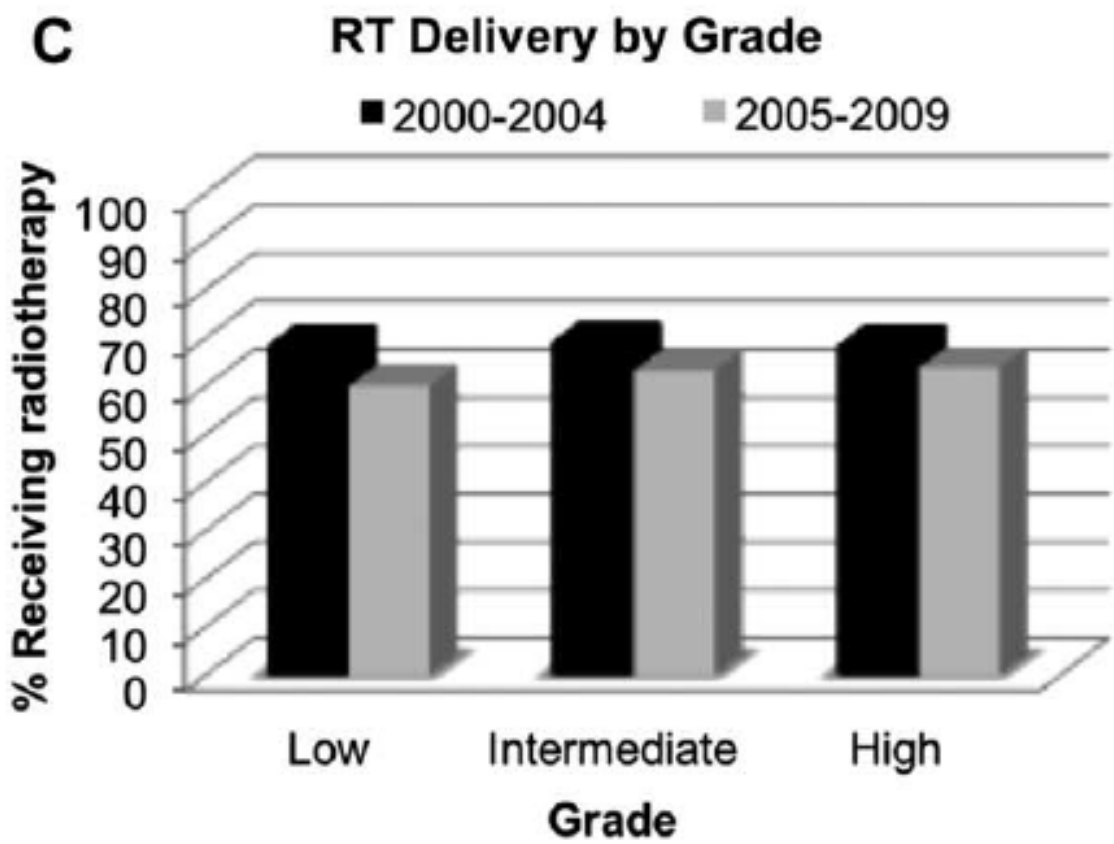
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## *...Possibili spiegazioni...*

- 1. Perplexità sull'adeguatezza del FUP**
- 1. Pubblicazione della metanalisi EBCTCG che evidenzia correlazione 4:1 tra  $RL_{5aa}$  e  $OS_{15aa}$**
- 2. Preferenza a parità di efficacia nell'adottare un trattamento che aggiunge o potenzia un approccio terapeutico piuttosto di un cambiamento che ne elimina uno**
- 3. Percezione delle pazienti di essere sottotrattate**
- 4. Molti di questi studi non forniscono informazioni su alcuni noti fattori predittivi di rischio di recidiva**
- 5. Questa opzione terapeutica non è supportata da inconfutabili certezze**
- 6. Contemporanea pubblicazione di studi di HF-WBRT e PBI**

## ...Conclusioni...

- Nelle pazienti > 65 aa, G1-G2, pN0, < 3 cm e ER+ la sola ormonoterapia è un'opzione terapeutica ragionevole (!!!  
**Compliance OT e Tossicità OT)**

**Kunkler et al. The Lancet Oncology Vol 16 March 2015**

- Il contributo della RT è ininfluenza sul controllo locale nei pazienti >70aa pT1c cN0 ER-positive; la sua omissione non impatta sulla mortalità cancro-relata. La RT riduce significativamente il rischio di IBTR solo nei pT2 (!!! **Bias**)

**Martelli et al. EJC 51 (2015) 1358-1364**

- L'istotipo biomolecolare è un fattore prognostico di recidiva locoregionale ma non predittivo di risposta al trattamento radiante perché l'interazione del tipo di trattamento con l'istotipo biomolecolare non è significativa.

**Fei-Fei Liu et al. JCO 2015 33: 2035-2040**





...GRAZIE!