



Gruppo Regionale
AIRO APPULO-LUCANO

La Radioterapia nel cancro della mammella: indicazioni e tecnica

I Convegno
del Gruppo Regionale AIRO APPULO-LUCANO

Taranto, 19 giugno 2010

Auditorium Ospedale SS. Annunziata
Padiglione Vinci

IL TIMING CHIRURGIA- RADIOTERAPIA

Dott. G. Bove

S.C. Radioterapia

Azienda Ospedaliero-Universitaria OO.RR. - Foggia

TARANTO, 17 GIUGNO 2010

E' unanimemente confermato che la Radioterapia riduce il rischio di recidiva loco-regionale nei tumori della mammella sottoposti a chirurgia conservativa e in casi localmente avanzati dopo mastectomia.

Non altrettanto chiaro è se l'intervallo di tempo tra chirurgia e radioterapia costituisca un fattore di rischio per la recidiva locale.

Problematiche

- ◆ Dati limitati e risultati contrastanti
- ◆ Per la maggior parte retrospettivi (problematiche etiche)
- ◆ Differenti terapie adiuvanti
- ◆ Differenti dosi di RT
- ◆ Differenti caratteristiche delle pz

Il timing Chirurgia – Radioterapia è ancora controverso

Razionale di una RT “precoce”

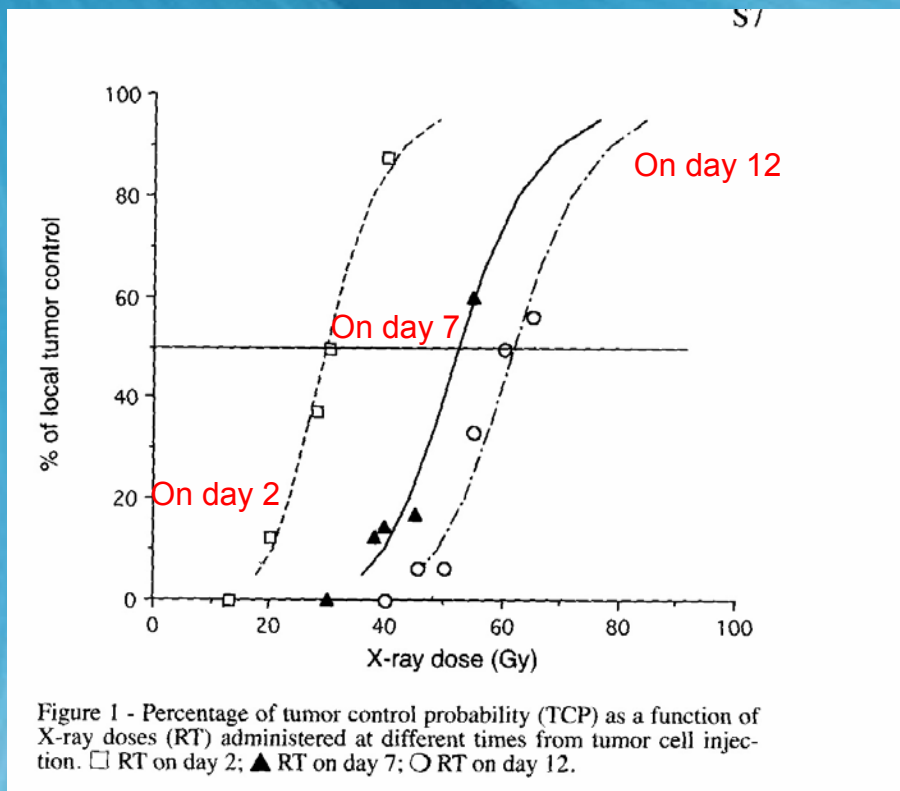
- ♦ La probabilità di eradicare il tumore con la RT è correlata al numero di cellule clonogene

Radiother Oncol 83 304–310, 2007

- ♦ La probabilità del controllo locale è inversamente correlata al volume tumorale

Radiother Oncol 1991;20:24–9

RT is expected to be the more efficacious the less the residual tumour burden, therefore, a long interval after breast surgery could theoretically lead to an increased residual tumour growth and, eventually, to poorer results.



Razionale di una RT "precoce"

There are abundant clinical and experimental data to indicate that the **chance of eradicating** a tumor with radiation **decreases** with increasing **tumor size**.

Delay would be expected to have the **most effect on the local control** of **fast-growing tumors**.

There are also reasons to suspect that **delay in initiating RT** may **increase** the risk of **distant metastasis**.

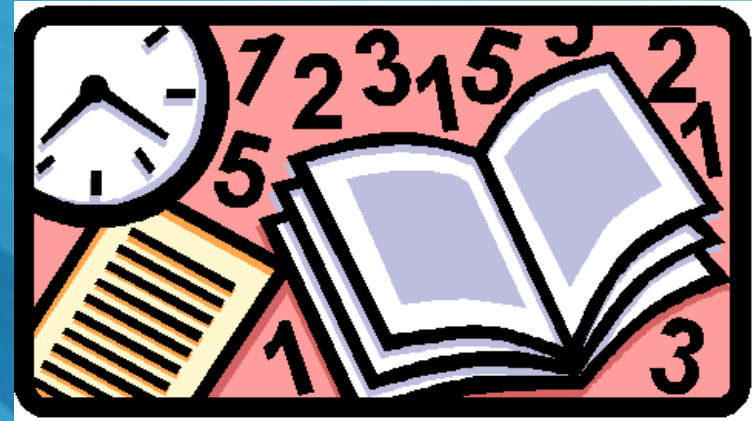
The development of a **local recurrence** is associated with an increased risk of distant metastasis.

There is increasing **evidence** that **preventing loco-regional failure** with RT **decreases the risk of distant metastasis** in breast cancer.



... La radioterapia, per essere efficace, deve essere fatta subito...

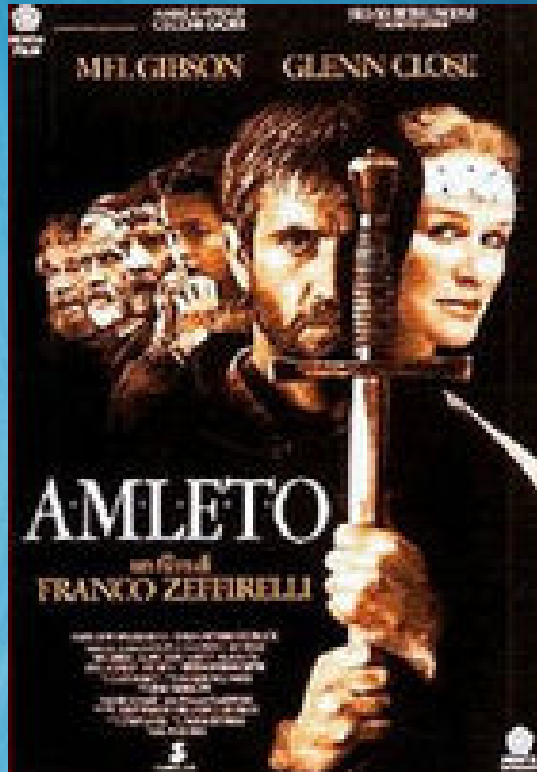
L	M	M	G	V	S	D
26	27	28	29	30	31	1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31	1	2	3	4	5





RT

CT



Prima CT?

Prima RT?

RT-CT?

RT dopo BCS

Study	No of patients	Follow-up (m)	RT delay (w)	LRR (%) 5-year	p-Value
Huang (4)	7,401	60	5–8 >8	5.8 9.1	<0.005
Benk (3 (abstract), 21)	482	68	8 14	0% 7%	<0.05, HR = 1.08/m of delay (CI: 1.0004–1.16)
Vujovic (22, 23)	568	63.5	8–12 >12	7.8 3.8	>0.05
Nixon (24)	673	100	0–4 5–8 9–12	13 8 2	>0.05
Whelan (25)	400	101	<8 >8	8.4 12.4	>0.1
Bahena (26)	623	64	<4 5–8 >9	–	<0.05 for DFS in the >9 w group
Slotman (27)	508	68	25–50 50–75	2 (RT 25–50d) 5.4 (59–75) 10.3 (>75) 1.7 vs. 5.6 within 50d	<0.05
Hebert-Croteau (28)	1,062	84 (1y)7	<12 >12	HR: 1.75	0.052
Hershman (30)	13,907	60	<12 >12	HR: 3.84	<0.05
Mikeljevic (31)	7,800	–	<9 >9	RR: 1.49	<0.005 (delay of 20–26 w)

EFFECT OF TIME INTERVAL BETWEEN BREAST-CONSERVING SURGERY AND RADIATION THERAPY ON IPSILATERAL BREAST RECURRENCE

PETER J. FROUD, M.B., FRCPC,*†§ DONNA MATES, M.A.,*|| JEREMY S.H. JACKSON, Ph.D.,*¶
NORM PHILLIPS, M.A.,|| SANDRA ANDERSEN, CCHRA(C),*§ STEWART M. JACKSON, M.D., FRCPC, †||#
CICELY J. BRYCE, M.D., FRCPC,*||# AND IVO A. OLIVOTTO, M.D., FRCPC*†||#

1962 donne, non trattate con chemioterapia

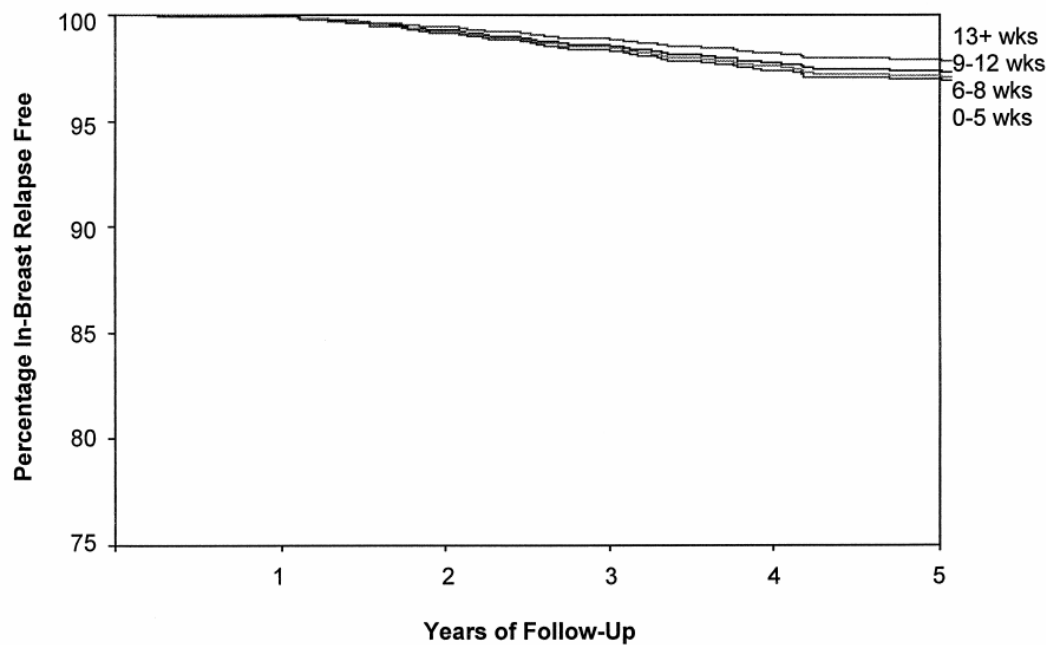


Fig. 4. Freedom from ipsilateral breast recurrence for the four intervals between definitive breast-conserving surgery and start of radiation therapy, corrected for grade and tamoxifen use. Interval groups are: 0–5 weeks, 6–8 weeks, 9–12 weeks, and 13 or more weeks. The multivariate comparisons between the shortest interval and the others did not attain statistical significance (0–5 vs. 6–8 weeks, $p = 0.872$; 0–5 vs. 9–12 weeks, $p = 0.665$; 0–5 vs. 13+ weeks, $p = 0.573$).

Even if delay does not cause higher rates of IBR or of systemic spread, we do not condone extensive delays before initiating RT. If nothing else, such delays cause anxiety and disruption to the lives of women and their families.

EFFECT OF TIME INTERVAL BETWEEN BREAST-CONSERVING SURGERY
AND RADIATION THERAPY ON IPSILATERAL BREAST RECURRENCE

PETER J. FROUD, M.B., FRCPC,*†§ DONNA MATES, M.A.,*|| JEREMY S.H. JACKSON, PH.D.,*¶
NORM PHILLIPS, M.A.,|| SANDRA ANDERSEN, CCHRA(C),*§ STEWART M. JACKSON, M.D., FRCPC, †||#
CICELY J. BRYCE, M.D., FRCPC,*||# AND IVO A. OLIVOTTO, M.D., FRCPC*||#

Cosa emerge dal lavoro di
Froud ?

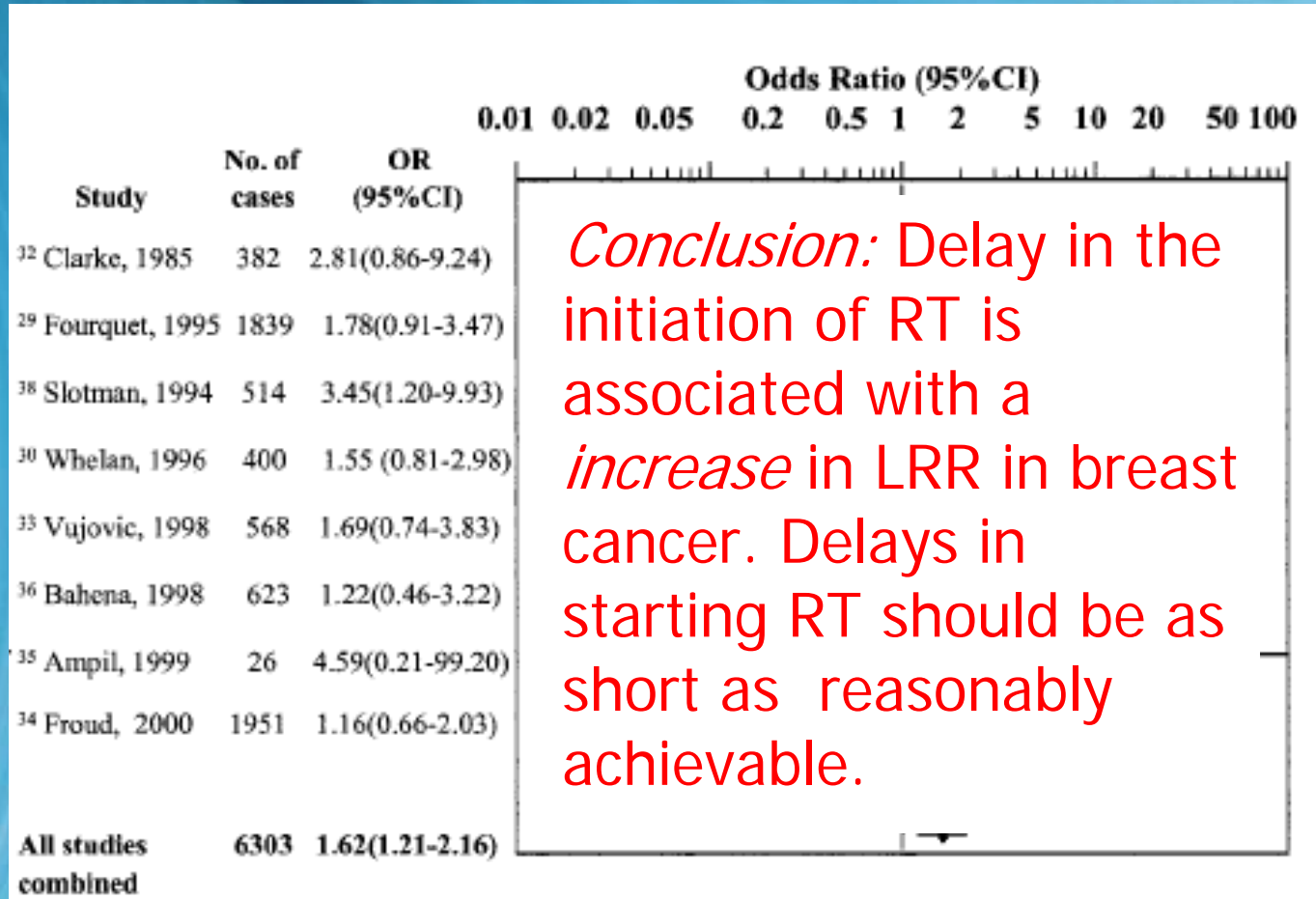
Età
G
tam
margini



rischio di ricaduta
locale

Does Delay in Starting Treatment Affect the Outcomes of Radiotherapy? A Systematic Review

A delay in RT → increase LR



5-year LRR from 5.8% in RT within 8 weeks to 9.1% in RT 9 and 16 weeks after surgery.

**Cosa dice la letteratura
più recente?**

**ELEVEN-YEAR FOLLOW-UP RESULTS IN THE DELAY OF
BREAST IRRADIATION AFTER CONSERVATIVE BREAST SURGERY IN
NODE-NEGATIVE BREAST CANCER PATIENTS**

OLGA VUJOVIC, M.D.,* EDWARD YU, M.D.,* ANIL CHERIAN, M.D.,† A. RASHID DAR, M.D.,*
LARRY STITT, M.Sc.,‡ AND FRANCISCO PERERA, M.D.*

Analisi retrospettiva 568 pts T1/T2 N0

- RT 0 - 8 sett. 201 pts
- RT 8 -12 sett. 235 pts
- RT 12-16 sett. 91 pts
- RT > 16 sett. 41 pts

ELEVEN-YEAR FOLLOW-UP RESULTS IN THE DELAY OF BREAST IRRADIATION AFTER CONSERVATIVE BREAST SURGERY IN NODE-NEGATIVE BREAST CANCER PATIENTS

OLGA VUJOVIC, M.D.,* EDWARD YU, M.D.,* ANIL CHERIAN, M.D.,† A. RASHID DAR, M.D.,*
LARRY STITT, M.Sc.,‡ AND FRANCISCO PERERA, M.D.*

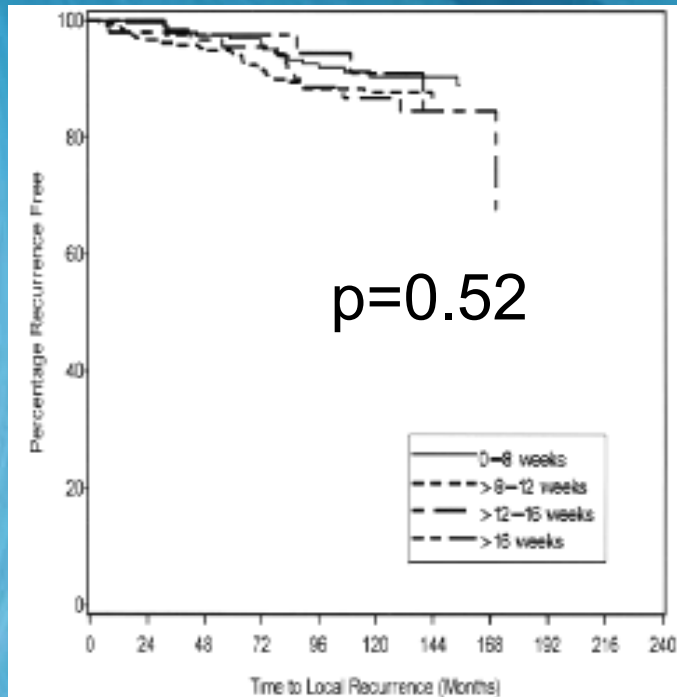


Fig. 1. Local recurrence as a function of surgery-radiotherapy interval.

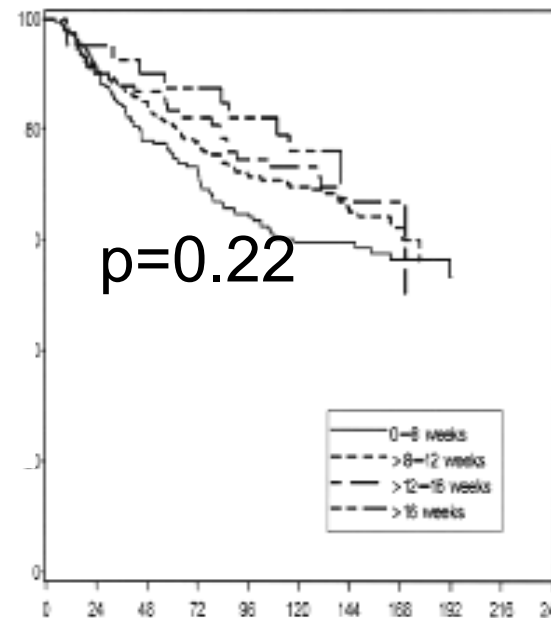


Fig. 2. Disease-free survival as a function of surgery-radiotherapy interval.

follow-up mediano 11,2 aa.

Conclusion: This retrospective study suggests that delay in the start of breast irradiation of up to 16 weeks from definitive surgery does not increase the risk of recurrence in node-negative breast cancer patients. The certainty of these results is limited by the retrospective nature of this analysis. © 2006 Elsevier Inc.

THE EFFECT OF TIMING OF RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY IN PATIENTS WITH POSITIVE OR CLOSE RESECTION MARGINS, YOUNG AGE, AND NODE-NEGATIVE DISEASE, WITH LONG TERM FOLLOW-UP

OLGA VUJOVIC, M.D.,* ANIL CHERIAN, M.B.B.S., M.R.C.S. (GLASG),[†] EDWARD YU, M.D.,*
A. RASHID DAR, M.D.,* LARRY STITT, M.Sc.,[‡] AND FRANCISCO PERERA, M.D.*

Patients **40 years** of age have an **increased local recurrence rate**, and these recurrences tend to occur **early**. Young patients should therefore undergo breast irradiation **as soon as possible** after surgery.

Patients with **positive or close resection margins** may have **higher local recurrence** rates that are delayed in appearance and that become apparent when breast irradiation is delayed.

The Effect of Delaying Adjuvant Radiation Treatment after Conservative Surgery for Early Breast Cancer

Giampiero Ausili Cèfaro, MD,* Domenico Genovesi, MD,* Rita Marchese, MD,*
Monica Di Tommaso, MD,* Federica Di Febo, MD,* Enzo Ballone, MD,[†] and
Marta Di Nicola, PhD[†]

Analisi retrospettiva su

802 tratte con chirurgia conservativa + radioterapia

- 393 con chemioterapia

tempo attesa <25 settimane = 183 pz

tempo attesa >25 settimane = 210 pz

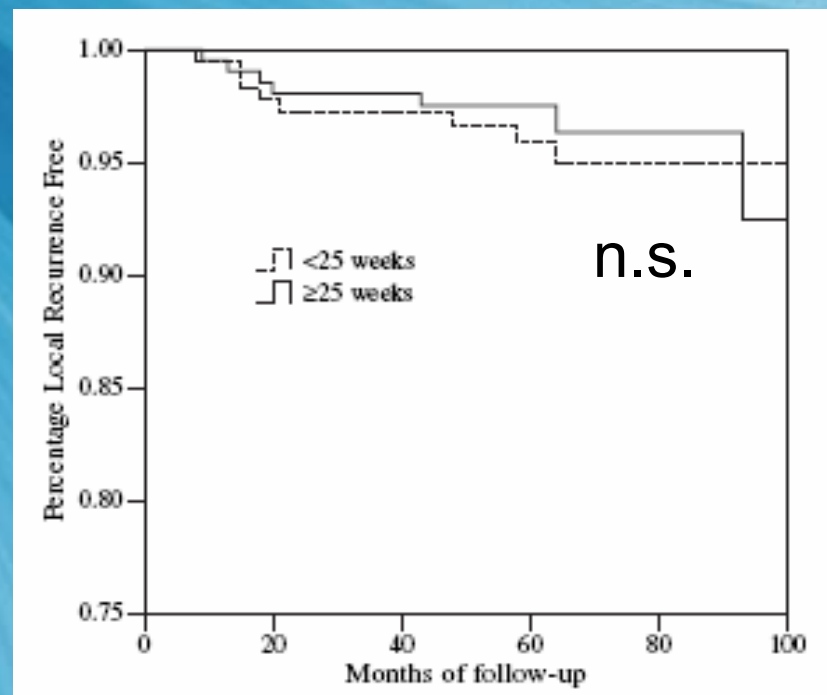
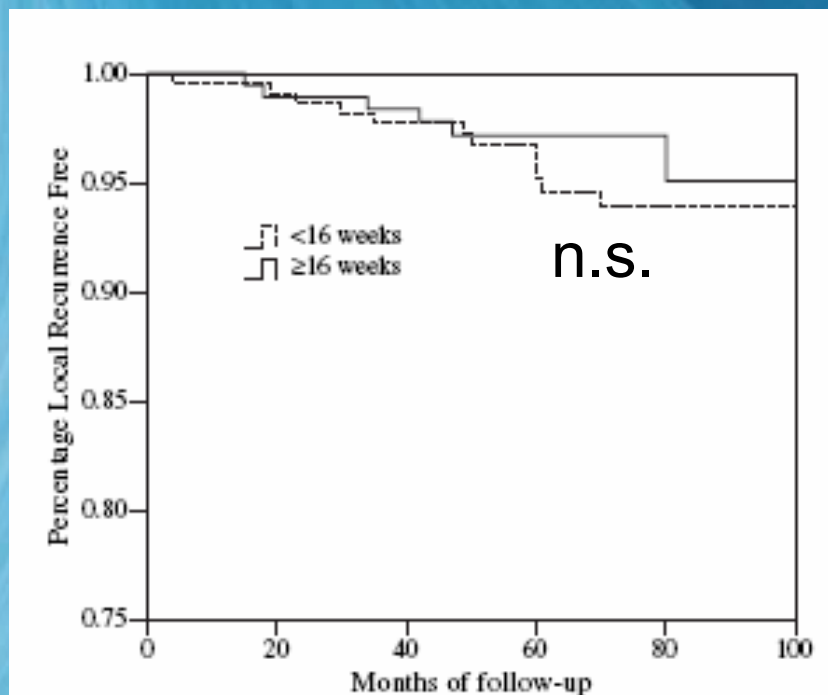
- 409 senza chemioterapia

tempo attesa <16 settimane = 222 pz

tempo attesa >16 settimane = 187 pz

The Effect of Delaying Adjuvant Radiation Treatment after Conservative Surgery for Early Breast Cancer

Giampiero Ausili Cèfaro, MD,* Domenico Genovesi, MD,* Rita Marchese, MD,*
Monica Di Tommaso, MD,* Federica Di Febo, MD,* Enzo Ballone, MD,[†] and
Marta Di Nicola, PhD[†]



Pz trattate senza chemioterapia

Pz trattate con chemioterapia

DELAY IN INITIATING ADJUVANT RADIOTHERAPY FOLLOWING BREAST CONSERVATION SURGERY AND ITS IMPACT ON SURVIVAL

DAWN L. HERSHMAN, M.D., M.S.,*†‡ XIAOYAN WANG, M.S.,† RUSSELL McBRIDE, M.P.H.,†
JUDITH S. JACOBSON, DR.P.H.,† VICTOR R. GRANN, M.D., M.P.H.,*†‡
AND ALFRED I. NEUGUT, M.D., PH.D.*†‡

Metanalisi di diversi studi su 13907 pts
con tumore della mammella stadio I-II

Tempi di attesa superiori a 3 mesi
erano associati a maggiore
mortalità globale e maggiore
mortalità cancro-specifica

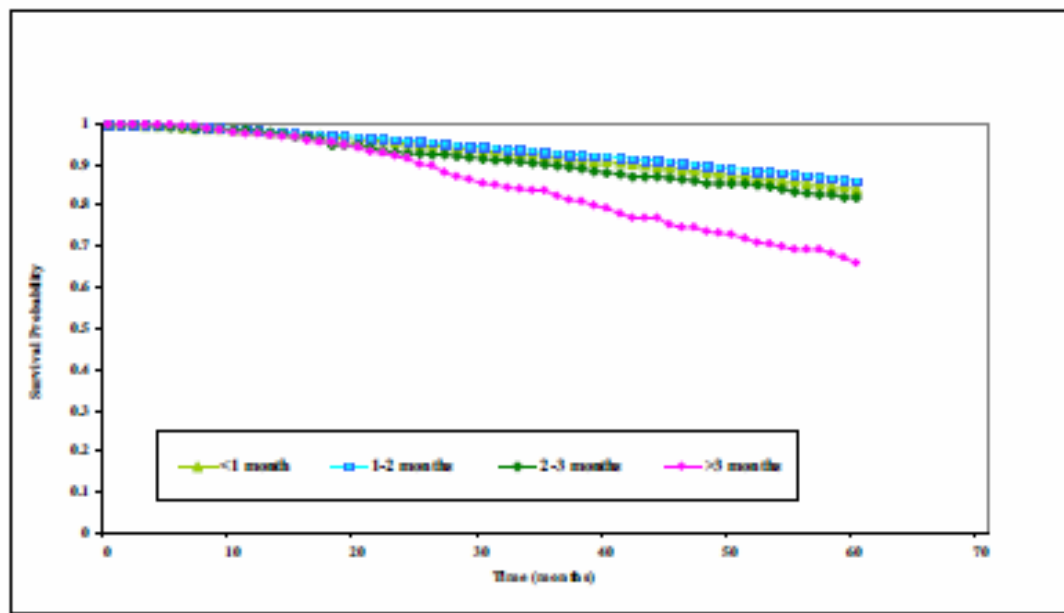
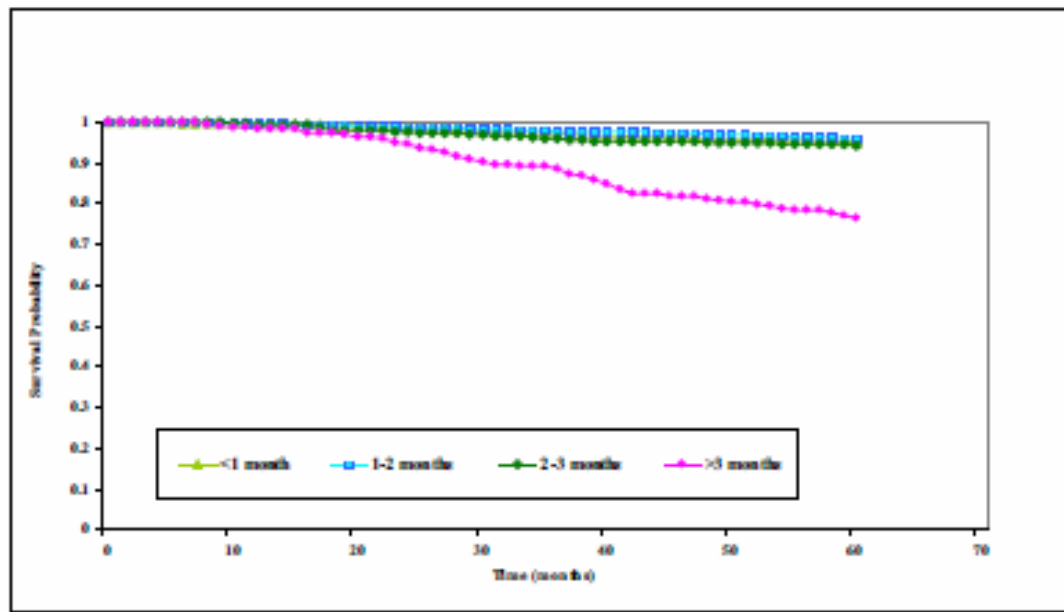


Fig. 1. Kaplan-Meier curves of breast cancer-specific survival (a) and overall survival (b) by time interval from lumpectomy to initiation of radiation therapy.



RT dopo mastectomia

- ◆ Non vi sono dati in letteratura che valutino l'intervallo di tempo tra mastectomia e RT adiuvante esclusiva.



RT + CT

Study	No of patients	Follow-up (m)	RT timing (m)	LRR (%)	p-Value	OS	p-Value
Hartsel (38)	84	62	<4 4	2 14	<0.05	-	>0.05
Buchholz (59)	105		>6 6	2 24	<0.05	80 52	0.016
Recht (60)	295	78	<4 4	5 35	<0.05	NP	NP
Leonard (61)	262	50?	<4 4-6 >6	5 3-5 2	>0.05	84 95 96	>0.05
Meek (62)	297			4 2	>0.05	91 83	NP
Yock (63)	279	84	<5 5-7 >7	5.5 4.8 7.4	>0.05	NP	NP
Dendale (64 (abstract))	283	83-136	NP CT first vs. RT first group	CT: 24.4 RT: 11	<0.03	9	-
Mc Cormick (65)	471	53-77		RT: 4 CT: 14 San: 4	>0.05		
Buzdar (66)	552	133			>0.05		
Recht, Bellon (67, 36)	244	135		38 (CT) 31 (RT)	>0.05	73 81	0.11 p: 0.41
Benchahal (68)	1831	102	After BCS After 3 CT After 6 CT	92 81.5 87.4 (L-DFS)	<0.001 NS in multivariate analysis	48.4 76.9	<0.001
Metz (69)	221	50	<2 2-6 >6	13 4 12	>0.05	NP	NP
Hickey BE (70) Cochrane Collaboration Study (Review)	244 853 concurrent (2 trials)		7 m vs. >7 m		>0.5		

	Number patients	BCS – RT interval	Local recurrence (%)
Recht	295	< 16 weeks	5 $P = 0.0001$
		> 16 weeks	35

The delay of more than 16 weeks after surgery in node-positive breast cancer pts treated with CT may result in an increased likelihood of local failure

	Number patients	BCS – RT interval	Local recurrence (%)	Disease free survival (%)	Overall survival (%)
Bucholz	105	< 24 weeks	2 <i>P</i> = 0.004	71	80
		> 24 weeks	24	48	52

After BCS, a delay of more than 6 months from diagnosis resulted in a higher rate of local failure, increased distant metastases and decreased overall survival.

	Number patients	BCS – RT interval	Local recurrence (%)
Hartsel	474	< 16 weeks	2 $P = 0.05$
		> 16 weeks	14

Delays in the initiation of irradiation are associated with an increased risk of local relapse The interval between breast surgery and Radiotherapy should be lower than 120 days

Dana Farber Cancer Institute

- ◆ 244 pz stadio I-II (1984-92) randomizzate dopo la BCT tra CT seguita da RT ("CT-first") e RT seguita da CT ("RT-first")
- ◆ RT: 45 Gy mammella + 16 Gy boost
- ◆ CT: CAMFP q 3 sett x 4 cicli
- ◆ I primi dati (a 5aa) sul NEJM nel 1996 non mostravano differenze su LR e OS ma evidenziavano un beneficio sul controllo delle metastasi a distanza per il braccio "CT-first"
- ◆ Nelle pz a rischio di metastasi è meglio somministrare prima la CT

Nessuna differenza in LR, DFS, DM e OS tranne...

Margin status (upfront/outback trial)

Med FU 135 months	Local relapse		Subset analysis
Margin <i>(CT-first vs RT-first)</i>	CT>RT	RT>CT	
Negative <i>(51% vs 50%)</i>	6%	13%	← Positive interaction
Close <i>(16% vs 23%)</i>	32%	4%	← RT benefit
Positive <i>(25% vs 16%)</i>	23%	20%	← Independent by sequence

Impatto del timing

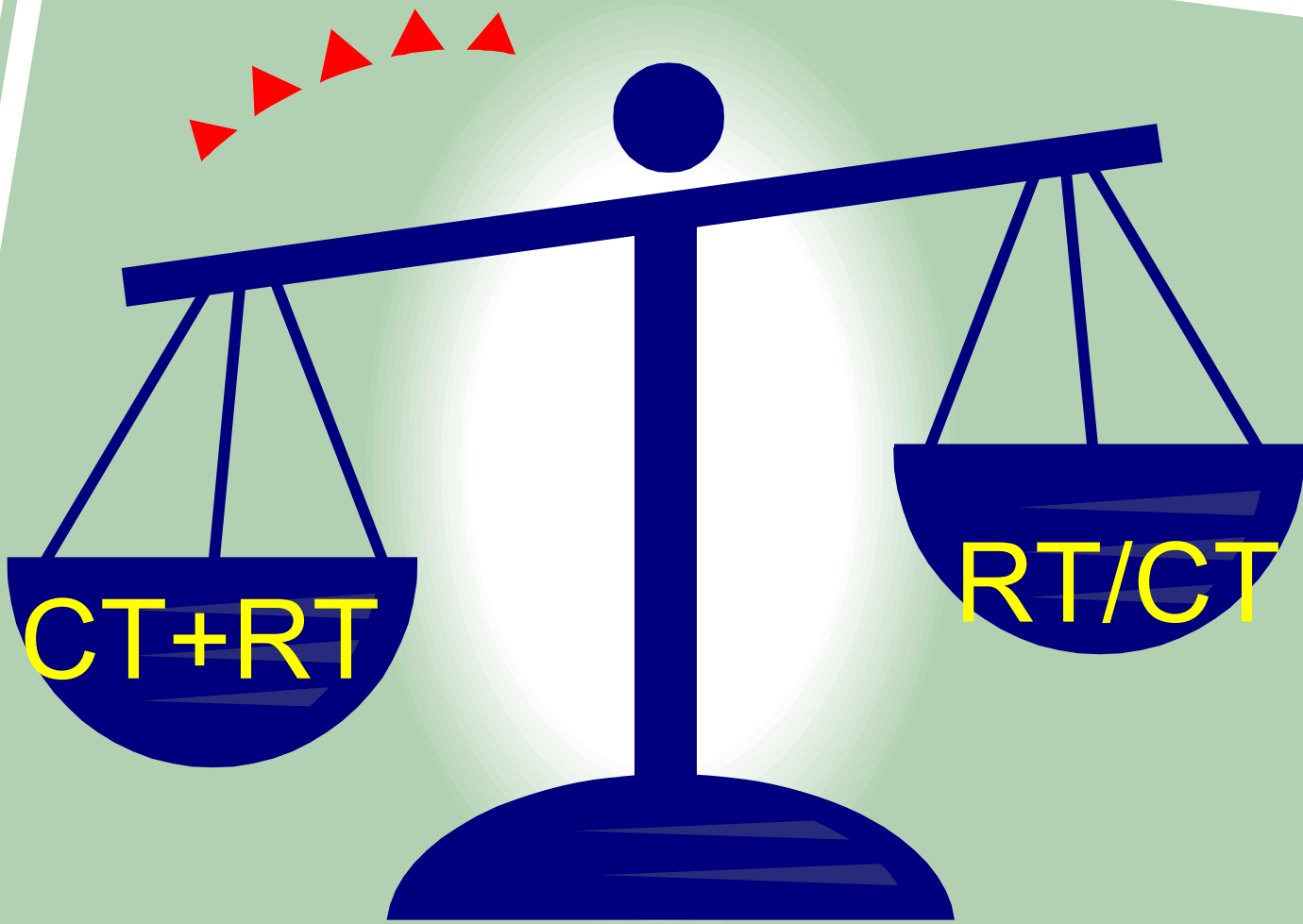
- ◆ La sequenza del trattamento dava risultati diversi sulle recidive locali in base allo stato dei margini ($p=0.01$)
- ◆ Margini negativi: basse % di LR sia nel braccio "CT-first" che nel braccio "RT-first"
- ◆ Margini "stretti": meglio la "RT-first"
- ◆ Margini positivi: alta % di LR in entrambi i gruppi

Implicazioni cliniche

- ◆ Con la RT immediata, margini negativi e “stretti” hanno una bassa % di LR
- ◆ Con la RT ritardata, i margini “stretti” sembrano avere un alto rischio di LR; pazienti con margini negativi non mostrano un aumentato rischio di LR se la RT viene ritardata ≥ 4 mesi (“CT-first”)
- ◆ Questo suggerisce che il ruolo della RT è diverso in diversi sottogruppi di pazienti

Trials randomizzati sul timing RT in pz chemiotrattati

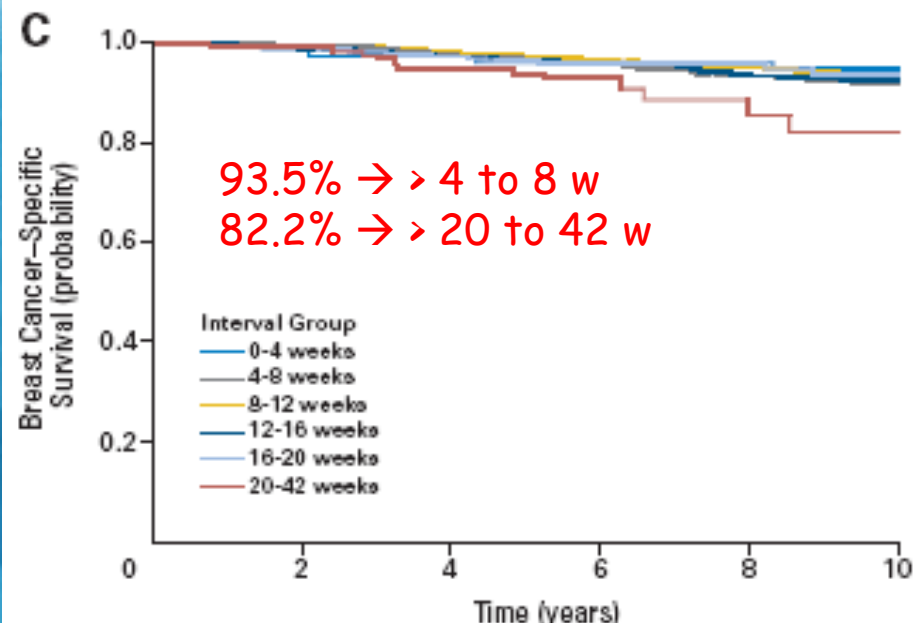
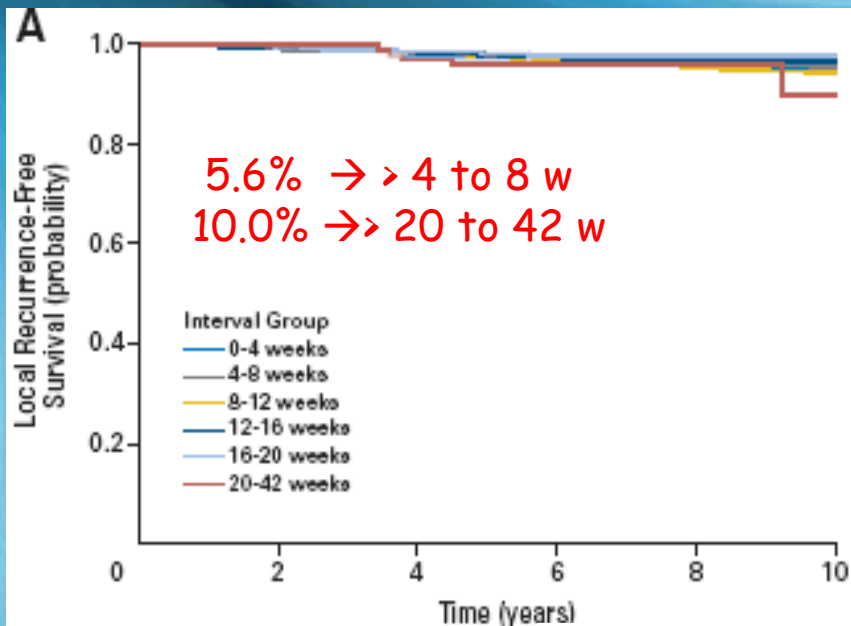
Autore	N° pz	Timing	BCS – RT intervallo	LR (%)	DFS (%)	OS (%)
Arcangeli	206	CMF+RT	< 2 mos	3	86.8	93.9
		CMF>RT	7 mos	4	87.1	94.7
Rouesse'	638	FNC+RT	< 2mos	3	83	NR
		FEC>RT	4 mos	7 <.001	79	NR
Toledano	706	FNC+RT	< 2 mos	4.5 N+ 4.5	80	91
		FNC>RT	6 mos	7.3 N+ 8.9 .02	80	90
Bellon	244	RT>CMFAP	< 2 mos	10	49	67
		CMFAP>RT	4 mos	11	54	72



Optimal timing for adjuvant radiation therapy in breast cancer A comprehensive review and perspectives

Pelagia G. Tsoutsou^{a,1}, Michael I. Koukourakis^{a,1}, David Azria^{b,1}, Yazid Belkacémi^{c,*,1}

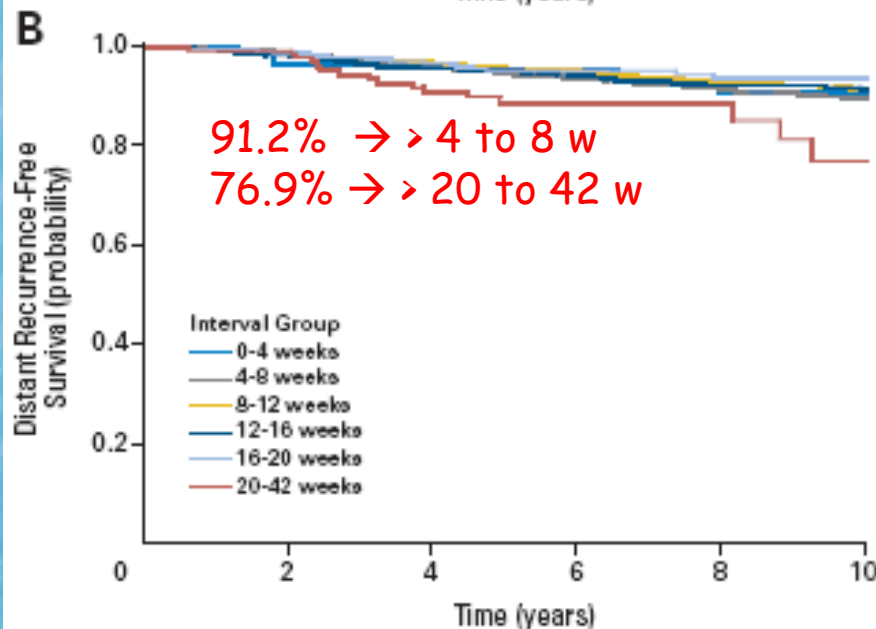
- **No randomized evidence** exists comparing RT delay as sole modality vs. no delay.
- A delay of **more than 8–12** weeks adversely affects local recurrence, when RT is administered as sole modality.
- Cases with a special interest with respect to RT delay represent **positive or close margins, young patients** and the possibility to overcome RT delay with a higher total dose.



VOLUME 27 • NUMBER 1 • JANUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Intervals Longer Than 20 Weeks From Breast-Conserving Surgery to Radiation Therapy Are Associated With Inferior Outcome for Women With Early-Stage Breast Cancer Who Are Not Receiving Chemotherapy

Ivo A. Olivetto, Mary L. Leprance, Pauline T. Truong, Alan Nichol, Tanya Berrang, Scott Tyklesley, François Gosselin, Caroline Speers, Elaine Wai, Caroline Holloway, Winkle Kwan, and Hagen Kennedy

6428 donne → T1-2, N0-1
BCS e RT, no CT

Linee Guida AIRO

La Radioterapia dei
Tumori della Mammella
-
Indicazioni e Criteri Guida



Gruppo di Lavoro AIRO per la Patologia Mammaria

- 2009 -

- Si ritiene utile iniziare la radioterapia nel più breve tempo possibile, non essendo identificabile una soglia limite

CLINICAL INVESTIGATION

Breast

**RADIOTHERAPY TIMING IN 4,820 PATIENTS WITH BREAST CANCER:
 UNIVERSITY OF FLORENCE EXPERIENCE**

LORENZO LIVI, M.D.,* SIMONA BORGHESI, M.D.,* CALOGERO SAEVA, M.D.,† ICRO MEATTINI, M.D.,*
 ANDREA RAMPINI, M.D.,* ALESSIA PETRUCCI, M.D.,* BEATRICE DETTI, M.D.,* ALESSIO BRUNI, M.D.,*
 FABIOLA PAIAR, M.D.,* MONICA MANGONI, M.D.,* LIVIA MARRAZZO, PH.D.,†
 BENEDETTA AGRESTI, M.D.,* LUIGI CATALIOTTI, M.D.,§ SIMONETTA BIANCHI, M.D.,¶
 AND GIAMPAOLO BITI, M.D.*

Table 2. Multivariate regression analysis to identify the major predictor factors of local breast relapse in series of 1,935 patients treated with radiotherapy without other systemic treatment

Parameter	Parameter estimate	p	HR	95% CI
Age*	-0.32128	0.0012†	0.725	0.597–0.880
pT*	-0.03172	0.7886	0.969	0.768–1.222
Positive nodes*	-0.46712	0.4736	0.627	0.175–2.249
Multifocal (yes)	0.10016	0.7472	1.105	0.601–2.032
Margins (positive)	0.89610	0.0004†	2.450	1.490–4.029
Boost (yes)	-0.52408	0.0017†	0.592	0.427–0.821
Timing*	0.13272	0.2561	0.876	0.696–1.101

Abbreviations: HR = hazard ratio; CI = confidence interval.

* Category at risk according to ordinal scale (Table 1).

† Statistically significant.



Timing RT e controllo locale

Non sono disponibili dati deducibili da **studi randomizzati**

I **risultati delle analisi sono discordanti** : alcuni autori non hanno riscontrato sicuro impatto del delay (Nixon 1994, Froud 2000, Vojovic 2006) altri viceversa si (Huang 2003, Benk 2004, Hebert-Croteau 2004, Tsoutsou 2009).

Diversi autori sottolineano **l'importanza dei fattori prognostici** (età, G, stato dei margini) nella determinazione del rischio di ricaduta locale (Froud 2000, Benk 2004, Vojovic 2006, Livi 2008).

Tutti sostengono che la RT deve essere iniziata tempestivamente o perché il ritardo aumento il rischio di ricaduta locale (Huang 2003, Benk 2004, Toutsou 2009) o perché l'attesa crea ansietà nella paziente, inficiando la qualità di vita (Froud 2000).

Timing RT e sopravvivenza

Solo un numero **limitato di studi** ha valutato la problematica ed i **risultati** sono spesso **inconclusivi e/o contraddittori**.

Diversi autori affermano che pur aumentando il rischio di ricaduta locale un ritardo nell'inizio della radioterapia **non peggiora la sopravvivenza** (Hebèrt-Croteau N, 2004, Chen Z, 2008, Tsoutsou P 2009 P).

Alcuni autori hanno riscontrato che **considerevoli waiting time possono peggiorare la Sopravvivenza** (Mikeljevic JS, 2004, Olivotto I, 2009).

Conclusioni

Non esiste evidenza clinica né ragioni teoriche per credere che esista una **soglia** sotto la quale il ritardo della RT adiuvante possa considerarsi sicuro.

Si potrebbe suggerire un inizio della RT **il più precocemente possibile, entro le 8-20 settimane** dalla chirurgia.

Il timing della RT può influenzare la recidiva locale, che tuttavia resta primariamente correlata ai fattori prognostici.

Un **inizio precoce** della RT potrebbe essere importante nelle **donne giovani** e/o con **margini "close"** (e/o altri **fattori di rischio?**), in cui si potrebbe considerare una RT-CT concomitante.

A large, leafless tree stands in a green field under a cloudy sky. The tree's branches are dark and intricate, forming a dense canopy. The sky is a mix of light and dark clouds, suggesting an overcast day. The foreground is a flat, green field. The overall mood is serene and contemplative.

GRAZIE