Associazione Italiana Radioterapia Oncologica

I Sessione

L'irradiazione convenzionale nella pratica clinica: frazionamento obsoleto o ancora attuale?

Moderatori: A. Di Grazia, A. Ciabattoni

Rapporteur: M.C. De Santis

Discussant: A. Fozza

IV ZOOM Journal Club 2014

Bologna, 20 Febbraio 2015

Azienda USL Valle d'Aosta-Vallée d'Aoste

Irradiazione convenzionale: frazionamento obsoleto o ancora attuale?

HFRT

Journal Club 2014

1. DCIS → HFRT +/- boost

2. Caratteristiche T e pazienti (mastectomia e N; classificazione biologiche e G; età e volume mammario)

3. TOX → cardiotossicità; ChT

DCIS: HFRT & BOOST

Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Cecilia Nilsson Antonis Valachis

Eskilstuna, Sweden

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Purpose: The purpose of this meta-analysis is to summarize the current evidence on the role of boost and the efficacy of hypofractionated radiotherapy in patients with ductal cancer in situ (DCIS) after surgery and grade the quality of evidence.

13 studies

Studies eligible investigated **efficacy of HFRT** (<u>any schedule</u>) vs **CFRT** (50 Gy/25 fr)

in DCIS pts or the **efficacy of boost in DCIS RT** (<u>HFRT or CFRT</u>) vs **no boost**

DCIS: HFRT & BOOST

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Cecilia Nilsson Antonis Valachis

LR: HFRT vs CFRT

4 studies: data on LR DCIS pts received **HFRT vs CFRT** (2534 patients)

NO difference in LR rate (OR: 0.78, 95% CI:0.58–1.03, p = 0.08)

Retrospective studies

DCIS: HFRT +/- BOOST

Contents lists available at ScienceDirect

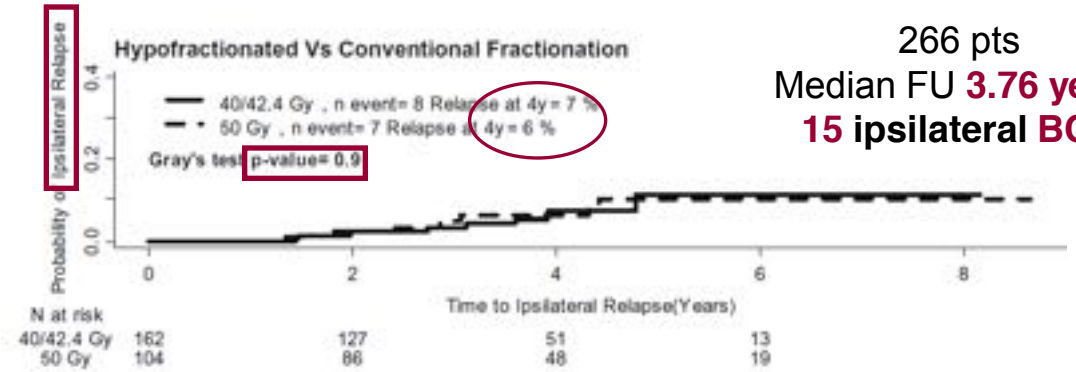
Radiotherapy and Oncology

Radiotherapy and Oncology 95 (2010) 317–320

Ductal carcinoma in situ

Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma in-situ

Deborah Williamson *University of Toronto, Canada*



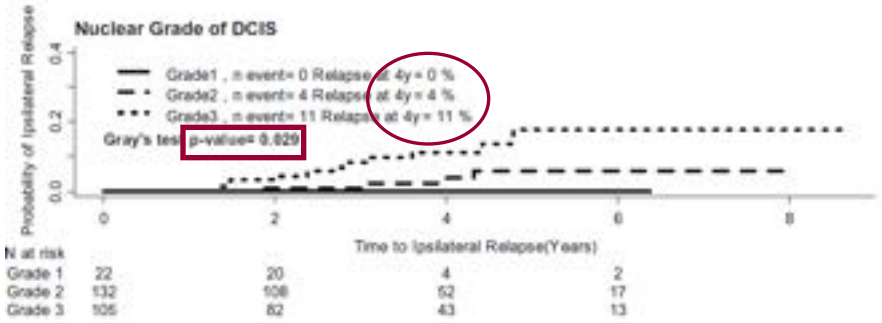
266 pts
Median FU **3.76 years**
15 ipsilateral BCR

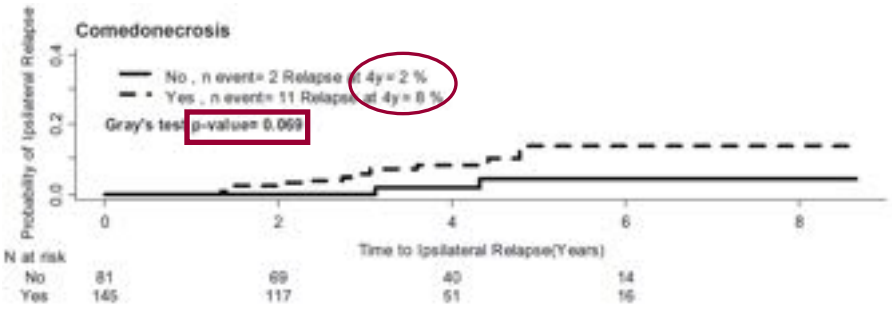
61% **39%**

Patient characteristics by treatment schedule.

	Variable	40 Gy/ 42.4 Gy	50 Gy	p-value
Age		58.4 ± 9.3	56.5 ± 9.6	0.16
Size in mm mean ± SD		17.5 ± 14.8	21.2 ± 16.8	0.05
Presentation *N* (row %)	Symptomatic/ incidental screening	28 (58%) 134 (61%)	20 (42%) 84 (39%)	0.69
Nuclear grade	1	17 (77%)	5 (23%)	0.31
	2	77 (58%)	55 (42%)	
	3	62 (59%)	43 (41%)	
Comedonecrosis	No	46 (57%)	35 (43%)	0.44
	Yes	90 (62%)	55 (38%)	
Multi-focal	No	129 (65%)	71 (36%)	0.13
	Yes	27 (53%)	24 (47%)	
Margin	<1 mm	26 (58%)	19 (42%)	0.3
	1–9 mm	79 (61%)	50 (39%)	
	>10 mm	11 (52%)	10 (48%)	
	Clear	45 (69%)	20 (31%)	

Univarite analysis





DCIS: HFRT +/- BOOST

Effect of Radiotherapy Boost and Hypofractionation on Outcomes in Ductal Carcinoma In Situ

Elaine S. Wai, BSc, MD, SM[1,2,3]; British Columbia, Canada

Cancer
January 1, 2011

957 pts
median FU 9.3 years

Adjuvant RT: 77% 44 Gy/16 fr
(482) 17% 50 Gy/25 fr.
If 45 Gy or less → 32% boost
More than 45 Gy → 16% boost
144 boost RT → 64% 7.5 Gy/3 fr

Patient, Tumor, and Treatment Characteristics

	No RT No. (%)	RT No boost No. (%)	RT+Boost No. (%)	P[a]
All subjects	475	338	144	
Age, y, median	57	59	56	
Age, y				.004
<50	143 (30)	106 (31)	44 (31)	
50-69	231 (49)	195 (58)	75 (52)	
>69	101 (21)	37 (11)	25 (17)	
Grade				<.001
1	171 (36)	53 (16)	23 (16)	
2	180 (38)	130 (38)	57 (40)	
3	97 (20)	128 (38)	59 (41)	
Unknown	27 (6)	27 (8)	5 (3)	
Size				<.001
<1.5 cm	343 (72)	179 (53)	75 (52)	
1.5 cm-4 cm	89 (19)	121 (36)	56 (39)	
>4 cm	29 (6)	29 (9)	12 (8)	
Unknown	15 (3)	9 (2)	3 (2)	
Comedo histology				<.001
No	354 (75)	153 (45)	77 (54)	
Yes	121 (25)	185 (55)	67 (46)	
Margin status				<.001
Positive	43 (9)	39 (12)	45 (31)	
Close	22 (5)	17 (5)	15 (10)	
Negative	377 (79)	279 (82)	80 (56)	
Unknown	33 (7)	3 (1)	2 (1)	
Re-excision				<.001
No	244 (51)	104 (31)	57 (40)	
Yes	231 (49)	234 (69)	87 (60)	
Axillary node dissection				<.001
No	282 (59)	231 (68)	111 (77)	
Yes	76 (16)	85 (25)	23 (16)	
Unknown	117 (25)	22 (7)	10 (7)	
Tamoxifen				<.001
No	460 (97)	307 (91)	139 (97)	
Yes	15 (3)	31 (9)	5 (3)	
Total radiotherapy dose				<.001
None	475 (100)	0 (0)	0 (0)	
≤45 Gy		262 (78)	129 (90)	
>45 Gy		76 (22)	15 (10)	

Results

	No RT	RT No Boost	RT+Boost	P[a]
LC				.065
5 Year	92%	96%	93%	
10 Year	87%	94%	91%	
BCSS				.16
5 Year	100%	100%	100%	
10 Year	98%	99.7%	100%	
OS				.013
5 Year	95%	98%	97%	
10 Year	85%	96%	94%	

Kaplan-Meier

Cox Regression Multivariate Analyses of Local Recurrence

	HR (95%CI)	P
Age, y		.17
≤70	1	
50-69	0.7 (0.2-1.2)	
<50	1.0 (0.6-1.8)	
Diagnosis year		.27
1985-1987	1	
1988-1991	1.5 (0.8-3.1)	
1992-1995	1.4 (0.6-2.9)	
1996-1999	0.9 (0.4-2.0)	
Grade		.007
1	1	
2	2.3 (1.2-4.3)	
3	1.1 (0.5-2.4)	
Unknown	1.4 (0.7-3.1)	
Size		.27
0.1-1.4	1	
1.5-4 cm	1.2 (0.7-1.9)	
>4 cm	1.9 (1.0-3.7)	
Unknown	1.36(0.5-3.5)	
Comedo histology		<.001
None	1	
Present	2.3 (1.4-3.7)	
Margin status		<.001
Negative	1	
Positive	2.7 (1.6-4.6)	
Close	3.1 (1.5-6.2)	
Unknown	3.6 (1.6-7.7)	
Tamoxifen		.3
No	1	
Yes	1.2 (0.4-2.4)	
Re-excision		<.001
No	1	
Yes	2.4 (1.5-3.8)	
Treatment		.004
BCS only	1	
RT ≤45 Gy, no Boost	0.4 (0.2-0.7)	
RT >45 Gy, no Boost	0.3 (0.1-0.6)	
RT ≤45 Gy, with Boost	0.5 (0.2-0.9)	
RT >45 Gy with Boost	0.8 (0.2-3.5)	

Hazard ratio (HR) greater than 1 indicates a higher risk of local recurrence compared with control group

DCIS: HFRT +/- BOOST

CLINICAL INVESTIGATION **Breast Cancer**

DUCTAL CARCINOMA *IN SITU*—THE INFLUENCE OF THE RADIOTHERAPY BOOST ON LOCAL CONTROL

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. e153–e158, 2012

PHILIP WONG, M.D., F.R.C.P.(C),* CHRISTINE LAMBERT, M.D., Montreal, QC, Canada

220 pts, 71% HFRT
42,5-45 Gy/16-20 fr + **7,5-16 Gy/3-8** fr boost
median FU **46 months**

8 LR

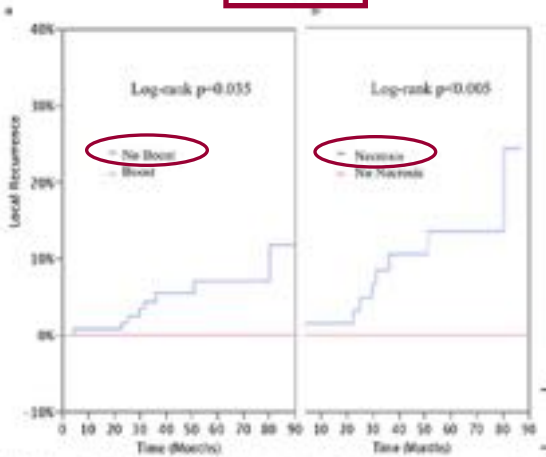


Fig. Kaplan-Meier curve for local recurrence of ductal carcinoma in situ (DCIS) patients. (a) Boost vs. no boost and (b) no boost patients with necrosis (+) vs. without necrosis (–).

Clinical characteristics of ductal carcinoma in situ (DCIS) patients by boost status

	No boost *N* = 141 (%)	Boost *N* = 79 (%)	Significance test and *p*
Age (y) at diagnosis			
≤50	34 (24%)	21 (27%)	Chi(1) = 0.1646
>50	107 (76%)	58 (73%)	*p* = 0.685
Median size of tumors (cm)	1 (0.01–1.13)	1 (0.73–1.12)	*Z* = –0.572*
			p = 0.5675
Tumor Grade 1	23 (16%)	12 (16%)	Chi(2) = 0.1678
Tumor Grade 2	65 (46%)	39 (49%)	*p* = 0.92
Tumor Grade 3	48 (35%)	26 (32%)	
Necrosis	35 (51%)	35 (44%)	Chi(1) = 0.9262
Necrosis yes	72 (49%)	72 (56%)	*p* = 0.34
Margin status			
Positive or <0.1 cm	51 (36%)	36 (46%)	Chi(2) = 61.405]
≥0.1 cm	125 (89%)	37 (47%)	*p* = 0.0001
Unknown	5 (4%)	4 (5%)	
ER status positive	76 (55%)	48 (61%)	Chi(2) = 0.7612
ER status negative	25 (18%)	11 (14%)	*p* = 0.683
Unknown	38 (27%)	20 (25%)	
VNP risk group			
High	1 (1%)	4 (5%)	Chi(2) = 10.25
Intermediate	66 (47%)	47 (60%)	*p* = 0.006
Low	70 (53%)	28 (35%)	
Whole breast radiation dose			
42.4–43 Gy	39 (28%)	29 (36%)	Chi(1) = 1.2006
45 Gy	80 (64%)	29 (38%)	*p* = 0.55
49–51 Gy	42 (28%)	21 (26%)	
No. with local recurrence	8 (6%)	0 (0%)	
Median follow-up (mo)	46.2	46.3	

Univariate analysis of ductal carcinoma *in situ* (DCIS) patients

Stratification	Univariate HR (95% CI) Event (LR)
Age (y) at diagnosis: ≤50	1.0
>50	0.54 (0.13–2.29)
Tumor size:	
≤1.5 cm	1.0
1.6–4.0 cm	0.68 (0.10–5.69)
≥4.1 cm	0.66 (0.08–5.63)
Histological grade	
1	1.0
2	1.89 (0.41–8.08)
3	1.69 (—)
Margin: Positive OR < 0.1 cm	1.0
≥0.1 cm	1.22 (0.24–6.17)
VNP category: Low	1.0
VNP category: Intermediate/high	0.46 (0.09–2.39)
Whole breast radiation dose	
42.4–43 Gy	1.0
45 Gy	0.15 (0.02–1.36)
50–51 Gy	0.60 (0.13–2.87)
<50 Gy	1.0
50–51 Gy	1.35 (0.32–5.69)

DCIS: HFRT +/- BOOST

Long-term Outcomes of Hypofractionation Versus Conventional Radiation Therapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ of the Breast

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1017–1024, 2014

Nafisha Lalani, MD Lawrence Paszat, MD, Toronto, Ontario, Canada

1609 pts
971(60%) CFRT
638(40%) HFRT(40-44 Gy/16 fr +/- boost)
median FU 9.2 years

Table 1 Patient characteristics

Characteristic	Whole cohort n = 1609	Radiation scheme: Conventional n = 971	Radiation scheme: Hypofractionation n = 638	P value
Age, y				
Median (IQR)	56 (49-65)	55 (49-64)	57 (50-66)	.009
<45	195 (12.1%)	122 (12.6%)	73 (11.4%)	.20
45-50	281 (17.5%)	181 (18.6%)	100 (15.7%)	
>50	1131 (70.3%)	666 (68.6%)	465 (72.9%)	
Unknown	2 (0.1%)	2 (0.2%)	0 (0.0%)	
Necrosis				
Absent	374 (23.2%)	225 (23.2%)	149 (23.4%)	.90
Present	949 (59.0%)	570 (58.7%)	379 (59.4%)	
Unreported	286 (17.8%)	176 (18.1%)	110 (17.2%)	
Nuclear grade				
Low	95 (5.9%)	55 (5.7%)	40 (6.3%)	.64
Moderate	672 (41.8%)	404 (41.6%)	268 (42.0%)	
High	591 (36.7%)	367 (37.8%)	224 (35.1%)	
Unreported	251 (15.6%)	145 (14.9%)	106 (16.6%)	
Multifocality				
Absent/unreported	1265 (78.6%)	746 (76.8%)	519 (81.3%)	.03
Present	344 (21.4%)	225 (23.2%)	119 (18.7%)	
Histologic subtype				
Solid	1074 (66.7%)	638 (65.7%)	436 (68.3%)	.14
Cribriform	332 (20.6%)	203 (20.9%)	129 (20.2%)	
Micropapillary	21 (1.3%)	9 (0.9%)	12 (1.9%)	
Other	50 (3.1%)	36 (3.7%)	14 (2.2%)	
Unreported	132 (8.2%)	85 (8.8%)	47 (7.4%)	
Margin status				
Negative	1002 (62.3%)	612 (63.0%)	390 (61.1%)	.68
Positive	256 (15.9%)	154 (15.9%)	102 (16.0%)	
Unreported	351 (21.8%)	205 (21.1%)	146 (22.9%)	
Tumor size, mm, median (IQR)	11.0 (7.0-17.0)	11.0 (8.0-18.0)	10.0 (7.0-15.0)	
Boost				
No	1120 (69.6%)	828 (85.3%)	292 (45.8%)	<.001
Yes	489 (30.4%)	143 (14.7%)	346 (54.2%)	
Tamoxifen use	Unknown			

Table 2 Outcomes in a Population of Women with DCIS treated by Conventional Radiotherapy or Hypofractionated Radiotherapy after Breast-Conserving Surgery

	Conventional N = 971 (%)	Hypofractionation N = 638 (%)	P-value
Any Local Recurrence	125 (12.8%)	65 (10%)	.06
Invasive Local Recurrence	62 (6.4%)	35 (5.5%)	
DCIS Local Recurrence	63 (6.4%)	30 (4.5%)	
Local Recurrence–Free Survival			
5-year	90%	93%	0.03
10-year	86%	89%	
Invasive Local Recurrence–Free Survival			
5-year	96%	96%	0.25
10-year	92%	94%	
DCIS Local Recurrence–Free Survival			
5-year	94%	96%	0.06
10-year	93%	95%	

Table 3 Factors associated with the development of (any) local recurrence in a population of women with DCIS treated with breast-conserving surgery and radiation therapy: Propensity score adjusted multivariable analysis

Factor	Hazard ratio	95% CI	P Value
Radiation scheme			
Hypofractionated	0.8	0.5-1.2	.34
Conventional	1.0		
Age at diagnosis, y			
<45	2.4	1.6-3.4	<.0001
45-50	1.2	0.8-1.8	.29
>50	1.0		
Nuclear grade			
High	2.9	1.2-7.3	.02
Intermediate	2.7	1.1-6.6	.04
Unreported	1.5	0.6-3.8	.43
Low	1.0		
Margin status			
Positive	1.4	1.0-2.1	.05
Unreported	1.6	1.1-2.4	.01
Negative	1.0		
Multifocality			
Present	1.3	0.9-1.8	.15
Absent	1.0		
Boost			
Yes	1.7	0.7-4.3	.26
No	1.0		

DCIS: HFRT & BOOST

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Cecilia Nilsson Antonis Valachis

Conclusion: Hypofractionated radiotherapy seems to be a safe option in patients with DCIS after breast-conserving surgery while the addition of boost reduces the risk for local recurrence in the presence of positive margins. However, the level of evidence for these observations ranges between very low and low and the results of the ongoing randomized trials are necessary to confirm the results with higher level of evidence.

Quality of evidence for each outcome using the GRADE approach.

Outcome	No of studies (patients)	Quality assessment					Summary of findings			Quality of evidence
		Study limitations	Consistency	Directness	Precision	Publication bias	Odds Ratio (95% CI)	Heterogeneity		
								I^2, %	p value	
Local recurrence (boost vs. no boost)	12 (6943)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.91 (0.77–1.08)	0	0.47	Very low
Local recurrence (boost vs. no boost) positive margins	6 (811)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.56 (0.36–0.87)	43	0.12	Very low
Local recurrence (boost vs. no boost) Age < 50 years old	7 (1345)	Moderate	Presence of inconsistency	Direct	Imprecision	Undetectable	0.83 (0.62–1.11)	28	0.22	Very low
Local recurrence (hypofractionated RT vs. standard RT)	4 (2534)	Moderate	No inconsistency	Direct	Imprecision	Undetectable	0.78 (0.58–1.03)	0	0.89	Low

DCIS: HFRT
Conclusioni

- **Non evidenze radiobiologiche di diversa risposta del tumore in situ rispetto all'infiltrante a HFRT** ***(Mouw KW., Harris JR., The Breast 2012;22:129-136)***

- **NO DCIS nei trial randomizzati pubblicati → iso-efficacia HFRT vs SFRT in trial retrospettivi**

- **Non evidenze sul vantaggio del boost**

- **TRIAL ONGOING Phase III**
  - ✓ **BIG 3-07 (TROG 07.01)**
  - ✓ **RTOG 1005**

HFRT: mastectomia +/-N

RADIATION ONCOLOGY—ORIGINAL ARTICLE

Journal of Medical Imaging and Radiation Oncology • (2014)

Hypofractionated radiation treatment following mastectomy in early breast cancer: The Christchurch experience

Dong-Hwan I Ko,[1] Andrew Norriss,[2] Christopher R Harrington,[1] Bridget A Robinson[3,4] and Melissa L James[1]

Nelson, New Zealand

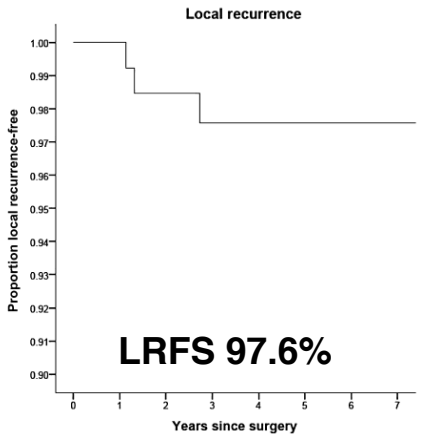
Acute toxicities from hypofractionated radiotherapy

	Number of patients (%)		
	Skin	Lethargy	Chest wall pain
Grade[a]			
No toxicity	17 (14.0)	52 (48.1)	74 (81.3)
Grade 1	91 (75.2)	52 (48.1)	13 (14.3)
Grade 2	13 (10.7)	4 (3.7)	3 (3.3)
Grade 3	0 (0.0)	0 (0.0)	1 (1.1)
Total graded	121	108	91

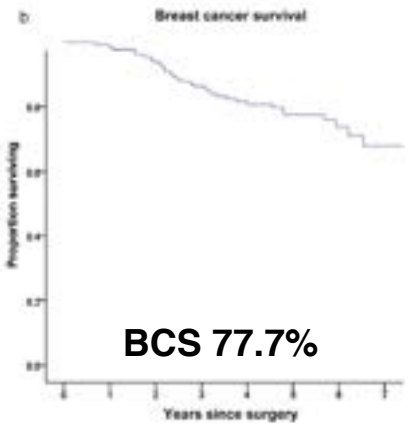
133 pts (2003-2008)
40Gy/16 fr
median FU **5 years**

Extent of radiotherapy	
Chest wall only	51 (38.3)
Chest wall and supraclavicular region	53 (39.8)
Chest wall, supraclavicular region and axilla	29 (21.8)

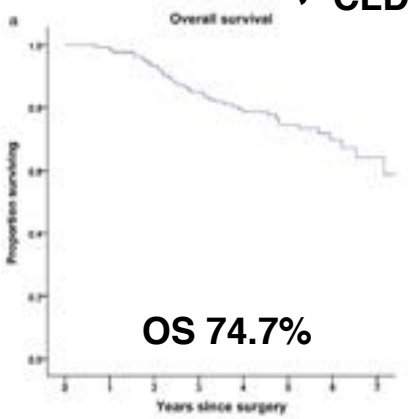
- ✓ **No dati tox subacuta – tardiva**
- ✓ **No braccio di confronto**
- ✓ **No OAR constraints**
- ✓ **CLD <3 cm**



LRFS 97.6%



BCS 77.7%



OS 74.7%

HFRT: mastectomia +/- N background

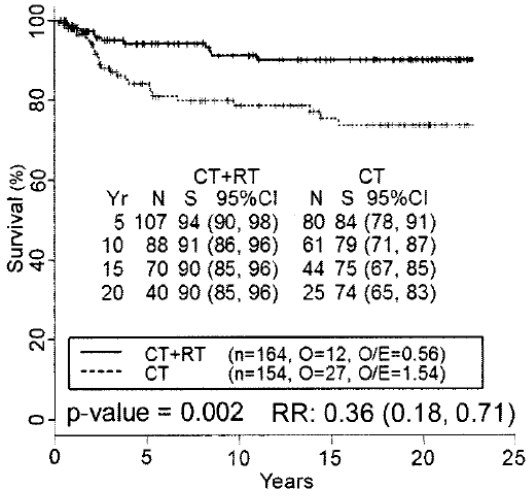
Locoregional Radiation Therapy in Patients With High-Risk Breast Cancer Receiving Adjuvant Chemotherapy: 20-Year Results of the British Columbia Randomized Trial

Journal of the National Cancer Institute, Vol. 97, No. 2, January 19, 2005

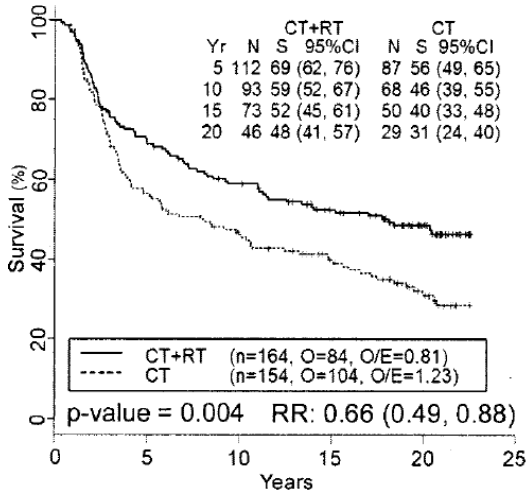
Joseph Ragaz, Ivo A. Olivotto, John J. Spinelli, Norman Phillips, Stewart M.

318 post mastectomy pts
(HF)RT vs **NO RT**
median FU **20 years**
35-37.5 Gy/16 fr

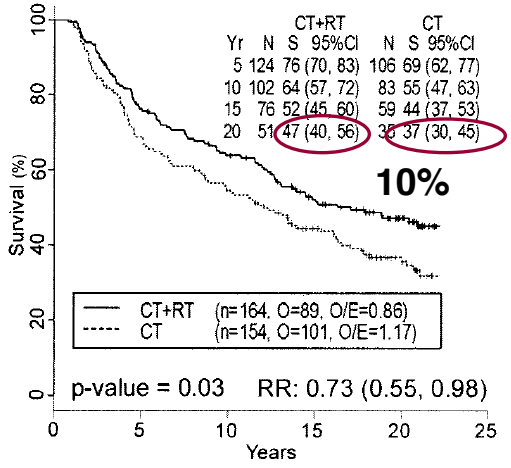
- ✓ **Campo diretto su CMI (sorgente Co60)**
- ✓ **RT a "sandwich" (fra 4 e 5 ciclo ChT)**
- ✓ **CMF schedule**



LRFS



BCFS



OS

Only 1 radiation pneumonitis and 3 cardiac deaths among CT-RT pts
Arm edema in 15 (9,1%) CT-RT pts vs 5 (3.2%) in the CT alone pts

HFRT: mastectomia +/- N background

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials *Lancet Oncol* 2013; 14: 1086–94

- **116 (7%)** of 2215 pts in **START-B** received regional post **mastectomy and lymphatic radiation**

- **NO evidence of increased normal tissue effects** of the **brachial plexus, arm oedema, or shoulder stiff ness** with HFRT in patients who did receive lymphatic treatment

- Theoretical modelling of normal tissue effects predicts that **40 Gy in 15 fractions** should be **as safe as 50 Gy in 25 fractions** for all **normal tissues**

A more conservative approach might be to continue to use the standard regimen in patients who receive regional nodal irradiation after lumpectomy or mastectomy!

…on going trial: Chinese Academy of Medical Sciences NCT 00793962

HFRT: Tumor factors background

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

N Engl J Med 2010;362:513-20.

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D.

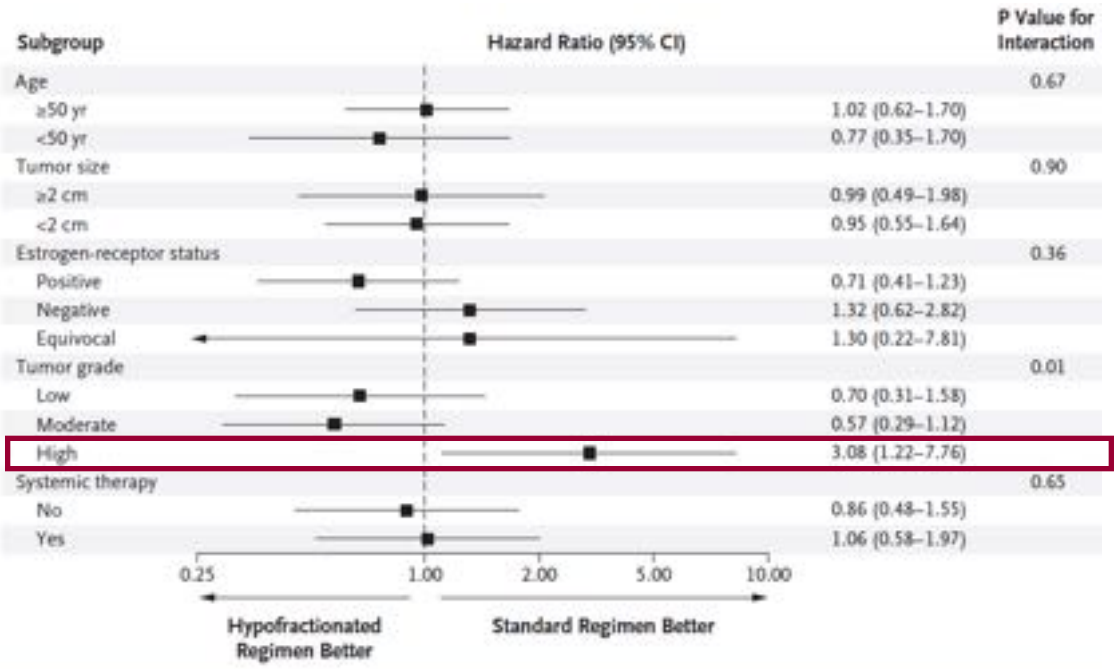


Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

✓ HFRT appeared to be less effective in patients with **high-grade tumors**.

✓ The cumulative incidence of LR at 10 years was **4.7% CFRT** compared with **15.6% in HFRT**

…but…evidence that **High-grade** tumors may be **more sensitive** to **accelerated schedules of RT!**

HFRT: Tumor factors

Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy

Annals of Oncology 25: 992–998, 2014

A. L. Bane[1,2*], T. J. Whelan[2], G. R. Pond[2], S. Parpia[2], G. Gohla[1], A. W. Fyles[3], J.-P. Pignol[3]

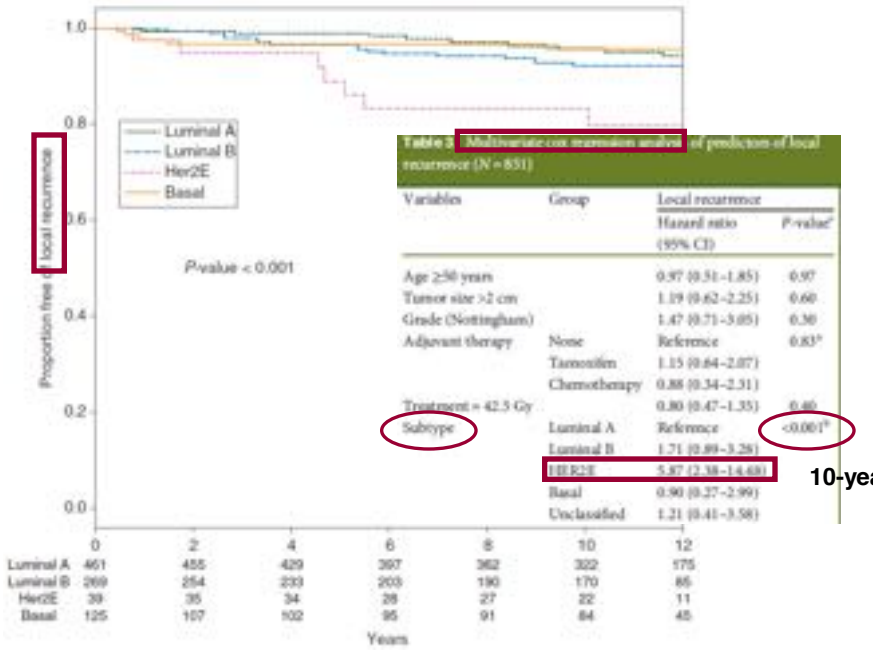
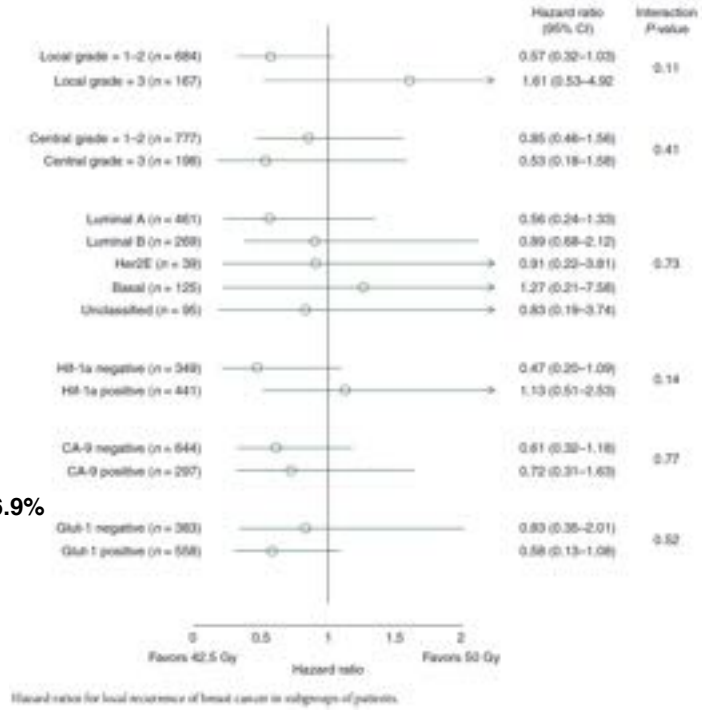


Table 3 Multivariate cox regression analysis of predictors of local recurrence ($N = 851$)

Variables	Group	Local recurrence Hazard ratio (95% CI)	P-value*
Age ≥50 years		0.97 (0.51–1.85)	0.97
Tumor size >2 cm		1.19 (0.62–2.25)	0.60
Grade (Nottingham)		1.47 (0.71–3.05)	0.30
Adjuvant therapy	None	Reference	0.83*
	Tamoxifen	1.15 (0.64–2.07)	
	Chemotherapy	0.88 (0.34–2.31)	
Treatment = 42.5 Gy		0.80 (0.47–1.35)	0.40
Subtype	Luminal A	Reference	<0.001*
	Luminal B	1.71 (0.89–3.28)	
	HER2E	5.87 (2.38–14.48)	
	Basal	0.90 (0.27–2.99)	
	Unclassified	1.21 (0.41–3.58)	

10-year LR 16.9%



Hazard ratios for local recurrence of breast cancer in subgroups of patients.

This result is in keeping with a recent analysis of the UK **START A and B trials:**

Tumor grade was not predictive of response to RT fraction size

HFRT: Cardiotossicità

Contents lists available at ScienceDirect

Radiotherapy and Oncology

Radiotherapy and Oncology xxx (2014) xxx–xxx

journal homepage: www.thegreenjournal.com

Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer

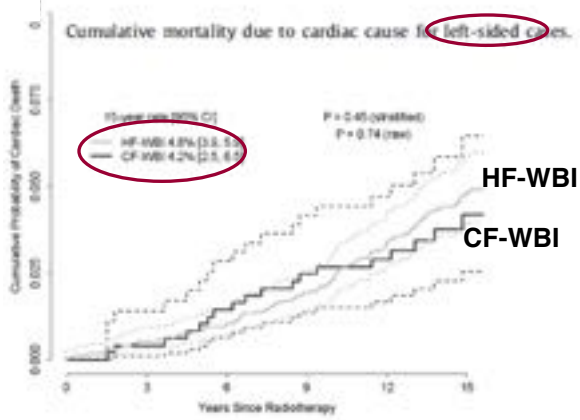
Vancouver, Canada

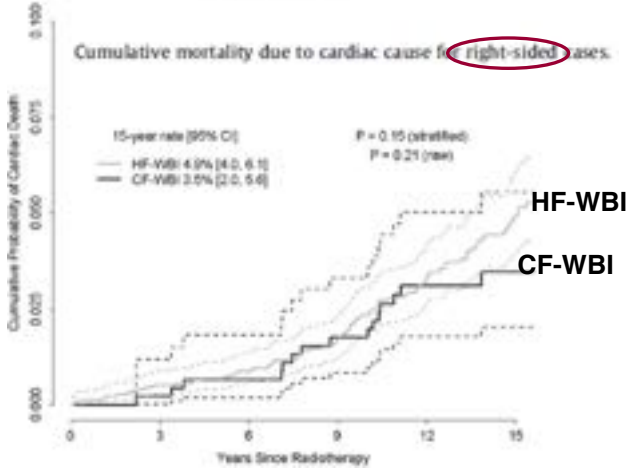
Elisa K. Chan [a], Ryan Woods [b], Sean Virani [c], Caroline Speers [d], Elaine S. Wai [e], Alan Nichol [f]

5334 pts (1980-1998)
Breast/chest wall alone
Median FU 14 years

Table 1
Patient, tumor and treatment characteristics for all patients who received either HF-WBI (hypofractionated whole breast radiotherapy) or CF-WBI (conventional fractionated whole breast radiotherapy).

Left-sided cases					Right-sided cases				
Variable	Statistic	CF-WBI (N = 485)	HF-WBI (N = 2221)	p-Value	Variable	Statistic	CF-WBI (N = 465)	HF-WBI (N = 2173)	p-Value
Age at diagnosis	Median (IQR)	58 (50–66)	58 (48–68)	0.82	Age at diagnosis	Median (IQR)	57 (49–66)	58 (47–68)	0.54
Summary stage	Stage 1	319 (66%)	1460 (66%)	0.99	Summary stage	Stage 1	296 (65%)	1473 (68%)	0.26
	Stage 2	166 (34%)	761 (34%)			Stage 2	159 (35%)	700 (32%)	
Grade	Grade 1	73 (15%)	403 (18%)	0.36	Grade	Grade 1	85 (19%)	390 (18%)	0.61
	Grade 2	233 (48%)	1044 (47%)			Grade 2	217 (48%)	1042 (48%)	
	Grade 3	148 (31%)	704 (32%)			Grade 3	127 (28%)	671 (31%)	
	Unknown	31 (6%)	70 (3%)			Unknown	26 (6%)	70 (3%)	
ER status	ER −ve	103 (21%)	421 (19%)	0.12	ER status	ER −ve	90 (20%)	452 (21%)	0.58
	ER +ve	298 (61%)	1482 (67%)			ER +ve	307 (67%)	1433 (66%)	
	Unknown	84 (17%)	318 (14%)			Unknown	58 (13%)	288 (13%)	
Hypertension	No	434 (89%)	2042 (92%)	0.08	Hypertension	No	413 (91%)	2021 (93%)	0.10
	Yes	51 (11%)	179 (8%)			Yes	42 (9%)	152 (7%)	
Diabetes	No	461 (95%)	2161 (97%)	0.01	Diabetes	No	429 (94%)	2126 (98%)	<0.0001
	Yes	24 (5%)	60 (3%)			Yes	26 (6%)	47 (2%)	
Other cardiac risks	No	467 (96%)	2168 (98%)	0.10	Other cardiac risks	No	445 (98%)	2134 (98%)	0.56
	Yes	18 (4%)	53 (2%)			Yes	10 (2%)	39 (2%)	
Non-cardiac comorbidities	No	470 (97%)	2151 (97%)	0.94	Non-cardiac comorbidities	No	447 (98%)	2109 (97%)	0.16
	Yes	15 (3%)	70 (3%)			Yes	8 (2%)	64 (3%)	
Surgery type	Lumpectomy	478 (99%)	2197 (99%)	0.003	Surgery type	Lumpectomy	460 (99%)	2102 (97%)	0.01
	Mastectomy	7 (1%)	24 (1%)			Mastectomy	5 (1%)	71 (3%)	
Boost	No	311 (64%)	1598 (72%)	0.001	Boost	No	266 (58%)	1633 (75%)	<0.0001
	Yes	174 (36%)	623 (28%)			Yes	199 (42%)	540 (25%)	
Hormones	No	315 (65%)	1437 (65%)	0.79	Hormones	No	287 (63%)	1476 (68%)	0.04
	Yes	166 (34%)	779 (35%)			Yes	167 (37%)	688 (32%)	
	Unknown	<5 (<1%)	5 (0.2%)			Unknown	<5 (<1%)	9 (0.4%)	
Chemotherapy	No	375 (77%)	1688 (76%)	0.54	Chemotherapy	No	363 (80%)	1645 (76%)	0.06
	Yes	110 (23%)	533 (24%)			Yes	92 (20%)	528 (24%)	
T stage	<2 cm	366 (75%)	1689 (76%)	0.79	T stage	<2 cm	352 (77%)	1698 (78%)	0.72
	>2 cm	119 (25%)	532 (24%)			>2 cm	103 (23%)	475 (22%)	
N stage	0 nodes +ve	388 (82%)	1739 (78%)	0.51	N stage	0 nodes +ve	350 (77%)	1709 (79%)	0.09
	>1 nodes +ve	75 (15%)	359 (16%)			>1 nodes +ve	87 (19%)	339 (16%)	
	Unknown	12 (2%)	123 (6%)			Unknown	18 (4%)	125 (6%)	
Year of diagnosis	1990–1992	137 (28%)	562 (25%)	0.11	Year of diagnosis	1990–1992	133 (29%)	551 (25%)	0.11
	1993–1995	173 (36%)	746 (34%)			1993–1995	160 (35%)	745 (34%)	
	1996–1998	175 (36%)	913 (41%)			1996–1998	162 (36%)	877 (40%)	





HFRT: Cardiotossicità

Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer

Elisa K. Chan [a], Ryan Woods [b], Sean Virani [c], Caroline Speers [d], Elaine S. Wai [e], Alan Nichol [f],

Retrospective study:

- ✓ **Popolazione** totalmente **non selezionata**, lungo sopravvivente
- ✓ Disponibilità di **dati clinici (co-morbidità)** di tutte le pz e legame di essi con i dati di sopravvivenza (pochissima perdita di dati al FU)
- ✓ **Cause di morte precisamente classificate** e codificate per nomenclatura ICD, così come le cause di ospedalizzazione pre RT → possibilità valutare le differenze cardiache al baseline che avrebbero potuto condizionare la mortalità cardiaca non RT correlata
- ✓ Più **grande n° pz** e più **lungo FU** dei trial randomizzati → maggior incidenza eventi cardiaci → eventi cardiaci avvenuti nelle pz irradiate non sono condizionati dal frazionamento e sono comunque eventi rari.

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Elisa K. Chan [a], Ryan Woods [b], Sean Virani [c], Caroline Speers [d], Elaine S. Wai [e], Alan Nichol [f],

✓ Fattori di rischio ed eventi nel database condizionati dalla **veridicità della codificazione** → codificatori blindati alla domanda dello studio → errore sistematico dovrebbe essere simile per i due gruppi.

✓ No CT simulation → **NO constraints - NO DVH** → dose media al cuore per RT sx 6.3 Gy vs 1.8 Gy a dx (*Mc Gale P, Darby SC - Radiother Oncol 2011;100:167-75*
Taylor CW, Bronnum D – Int J Radiat Oncol Biol Phys 2013;87:337-43)

✓ **No HER-2** → No Trastuzumab adiuvante → tempi attuali potrebbe aumentare la mortalità cardiaca aumentando la sopravvivenza cancro correlata (pz possono morire più facilmente per altre cause compreso eventi cardiaci)

HFRT: Cardiotossicità background

Modern Hypofractionation Schedules for Tangential Whole Breast Irradiation Decrease the Fraction Size-corrected Dose to the Heart

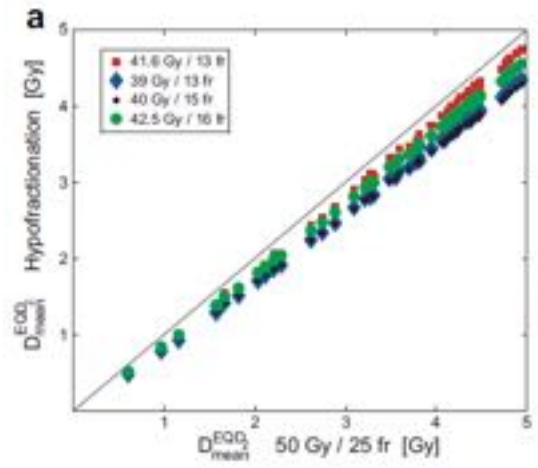
A.L. Appelt I.R. Vogelius S.M. Bentzen

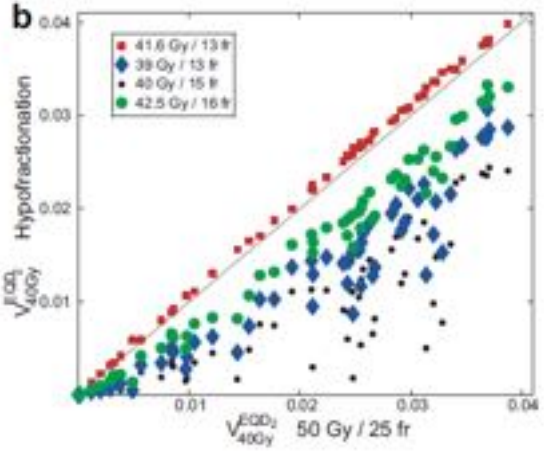
Clinical Oncology 25 (2013) 147–152

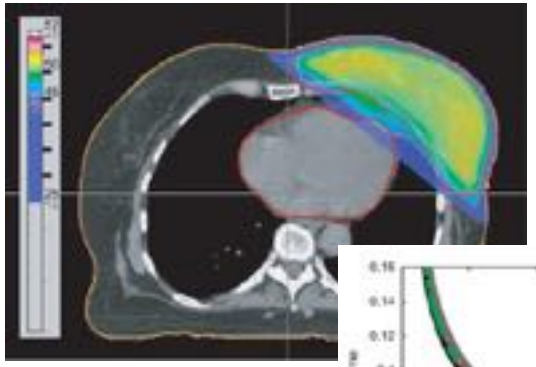
Fractionation schedules

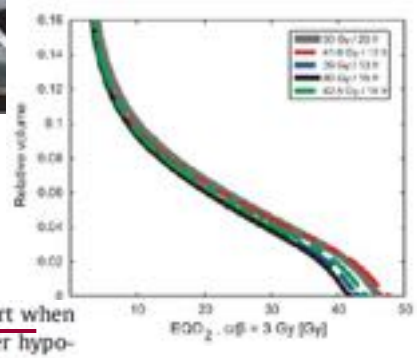
Schedule	Reference	EQD_2, $\alpha/\beta = 3$	EQD_2, $\alpha/\beta = 1$
50 Gy/25 fractions	(normofractionation)	–	–
41.6 Gy/13 fractions	START A_1	51.6 Gy	58.2 Gy
39 Gy/13 fractions	START A_2	46.8 Gy	52.0 Gy
40 Gy/15 fractions	START B	45.3 Gy	48.9 Gy
42.5 Gy/16 fractions	Whelan *et al.* [2] (Canadian)	48.1 Gy	51.8 Gy

Results: For $\alpha/\beta = 3$ Gy, $V_{40\ Gy}^{EQD_2}$ favours hypofractionation for 40 Gy/15 fractions, 39 Gy/13 fractions and 42.5 Gy/16 fractions, but not for 41.6 Gy/13 fractions. All of the hypofractionation schedules result in lower $D_{mean}^{EQD_2}$ compared with normofractionation. These results hold as long as $\alpha/\beta \gtrsim 1.5$ Gy. If the heart is blocked from the treatment beam, the fraction size-corrected dose is lower for the first three hypofractionation schedules, compared with normofractionation, even for $\alpha/\beta = \sim 1$ Gy.









Conclusion: For standard tangential field whole breast irradiation, most of the examined hypofractionation schedules are estimated to spare the heart when compared with normofractionation. The dose to the heart, adjusted for fraction size using the linear quadratic model, will generally be lower after hypofractionated compared with normofractionated schedules, even for very low values of α/β.

HFRT: Cardiotossicità

Conclusioni

✓ **NO maggior mortalità cardiaca in trial randomizzati di HFRT**

✓ **La maggior parte delle schedule di HFRT risultano radiobiologicamente inferiori in termini di cardio-tossicità rispetto a CFRT**

✓ **Comunque fondamentale proteggere il cuore indipendentemente dal frazionamento e dal lato sede del T**

HFRT: Chemioterapia

Adjuvant chemotherapy and acute toxicity in hypofractionated radiotherapy for early breast cancer

World J Clin Cases 2014 November 16; 2(11): 705-710

Vassilis Kouloulias, Anna Zygogianni, Efrosini Kypraiou, John Georgakopoulos, Zoi Thrapsanioti, Ivelina Beli

Table 2 Incidence of acute skin toxicity in terms of previous chemotherapy or not

		EORTC/RTOG radiation induced acute skin toxicity grade				Total
		0	1	2	3	
Chemotherapy	No	56/83 (67.5%)	18/83 (21.7%)	7/83 (8.4%)	2/83 (2.4%)	83
	Yes	16/33 (48.5%)	14/33 (42.4%)	2/33 (6.0%)	1/33 (3.0%)	33
Total		72/116 (62.1%)	32/116 (27.6%)	9/116 (7.8%)	3/116 (2.6%)	116

Table 3 Logistic regression analysis performed for analyzing the contribution of age, chemotherapy and radiotherapy fractions (19 *vs* 20) to the development of acute radiation induced skin toxicity

	Univariate analysis			Multivariate analysis		
	P	RR	95%CI	*P*	RR	95%CI
Age	0.31	-	-	0.41	-	-
Chemotherapy	0.05	2.35	1.01-5.52	0.057	-	-
19 *vs* 20 fractions	0.55	-	-	0.66	-	-

116 pts

Acute skin toxicitiy

50,54-53,2 Gy/19-20 fr

(2.66Gy/fr)

Acute skin toxicity

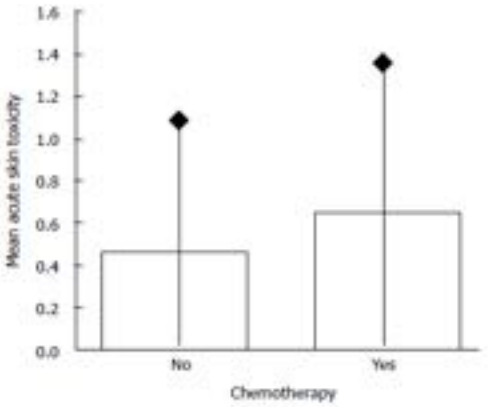


Figure 1 Mean acute skin toxicity score for patients undergone chemotherapy or not ($P = 0.109$, Mann Whitney test).

CMF & AC

HFRT: Chemioterapia

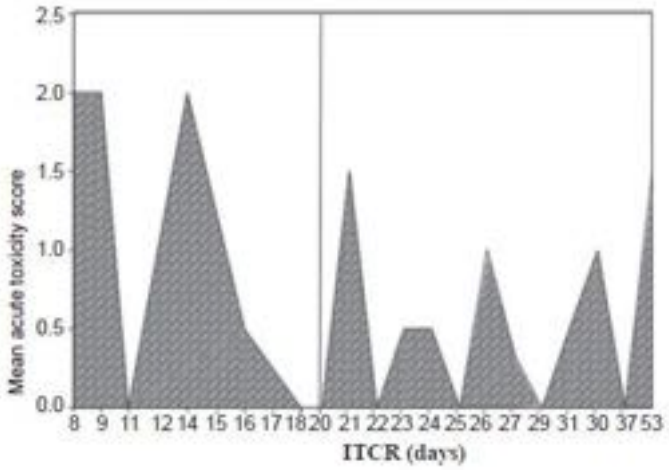
The Breast Journal
The Breast Journal, Volume 20 Number 1, 2014 74–78

The Impact of Intermediate Time between Chemotherapy and Hypofractionated Radiotherapy to the Radiation Induced Skin Toxicity for Breast Adjuvant Treatment

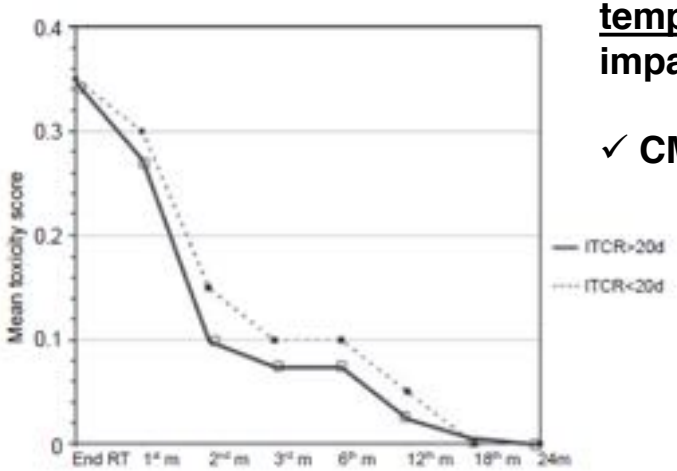
Anna Zygogianni, MD, PhD, Vassilios Kouloulias, MS, MD,

44 pts
mean FU 7 years
53 Gy/20 fr (2.65Gy/fr)

- ✓ **Unico trial che analizza <u>tempistica</u> CT- RT e suo impatto su tox**
- ✓ **CMF (6 cicli) schedule**



The cut-point of 20 days was selected due to the significant increase of the area under curve for cases later than 20 days ($p < 0.001$, Mann–Whitney test), as shown at the figure.



Kruskall-Wallis *($p < 0.05$)*

The toxicity according to the intermediate time between radiotherapy and chemotherapy.

HFRT: Chemioterapia background

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Lancet Oncol 2013; 14: 1086–94

N Engl J Med 2010;362:513-20.

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D.

✓ Systemic therapy (ChT/OT) used in a majority of pts in the published HFRT trial → few have specifically discussed this issue in relation to the **feasibility of combining** both approaches.

✓ In the **Ontario trial** only **11%** of patients received adjuvant **chemotherapy**, similarly, the **START A and B trials** between **22% and 35%** of enrolees received adjuvant chemotherapy.

Irradiazione convenzionale: frazionamento obsoleto o ancora attuale?

CONCLUSIONI

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 59–68, 2011

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria*

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

* For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade.

1) Età:

- " *Nearly al pts in the UK would receive HFRT and the agency NICE considers schemes of* ***50 Gy/25 fr or 40.05 Gy/15 fr*** *as standard RT for both BC conservative surgery and mastectomy* ***regardless of age at diagnoses*** **(*Montero A., The Breast 2014;23:299-309*)**

2) DCIS , mastectomia +/-N: propably safe…but no evidences.

- ON GOING phase III trial. **More conservative approach!** **(*Haviland SJ., Lancet Oncol 2013;14:1086-94*)**

Irradiazione convenzionale: frazionamento obsoleto o ancora attuale?

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3) ChT:

- *"There is **no** clear **evidence** that chemotherapy has an **impact to acute skin toxicity** after an HFRT schedule. A **randomized trial is needed** for definite conclusions"* (***Kouloulias V., WJCC 2014;2(11):705-10***)
- *" When a hypofractionated irradiation schedule is used the **ITCR** should be **more than 20 days** from chemotherapy* (***Zygogianni A., The Breast Journal 2014;1:74-78***)

4) **Breast volume:**

- *"Major component of the large breast is adipose tissue: possibility that adipose tissue is more sensitive to RT "* ***(Goldsmith C., Radiother Oncol 2011 Aug;100(2):236-40***
- Criticità superabile con **ottimizzazione delle tecniche** (IMRT, prone position) per aumentare HI?! ***(Mulliez T., Radiother Oncol 2013 Aug;108(2):203-8)***

Irradiazione convenzionale: frazionamento obsoleto o ancora attuale?

CONCLUSIONI

Choosing Wisely: The American Society for Radiation Oncology's Top 5 list

Practical Radiation Oncology (2014) 4, 349-355

Table 1 American Society for Radiation Oncology (ASTRO) Top 5 list

1. **Don't initiate whole-breast radiation therapy as a part of breast conservation therapy in women age ≥50 with early-stage invasive breast cancer without considering shorter treatment schedules.**	• Whole-breast radiation therapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5-6 weeks, often followed by 1-2 weeks of boost therapy. • Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (approximately 4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.[5,6,12]


…GRAZIE!