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Ipofrazionamento: why not?

Lorenza Marino

REM radioterapia-IOM

Catania

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DICHIARAZIONE

Relatore: **Lorenza Marino**

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Randomized hypofractionation trials

Trial	Randomisation (Gy/fraction)	Percent 5 yr local relapse (95% CI)	% 10 yr local relapse (95% CI)
START-P [3,38]	50.0/25	7.9 (5.4–10.4)	12.1 (8.8–15.5)
	42.9/13	7.1 (4.6–9.5)	9.6 (6.7–12.6)
	39.0/13	9.1 (6.4–11.7)	14.8 (11.2–18.3)
START-A [13]	50.0/25	3.4 (2.3–5.1)	6.7 (4.9–9.2)
	41.6/13	3.1 (2.0–4.7)	5.6 (4.1–7.8)
	39.0/13	4.4 (3.1–6.2)	8.1 (6.1–10.7)
START-B [14]	50.0/25	3.3 (2.4–4.6)	5.2 (3.9–6.9)
	40.0/15	1.9 (1.2–3.0)	3.8 (2.7–5.2)
Ontario [5,39]	50.0/25	3.2[a]	6.7[b]
	42.5/16	2.8[a]	6.2[b]

	Ontario [5,39]
Years accrual	1993–1996
Total number of p	1234
Standard arm (Gy/	50/25/5
Test arm A (Gy/fr/	42.5/16/3.1
Test arm B (Gy/fr/	n/a
Mean age (years)	Not reported
Node+ (%)	0
Mastectomy (%)	0
Tumour size ≥T2 (	20.0[b]
Boost (%)	0
Chemotherapy (%)	11
Regional radiothe	0

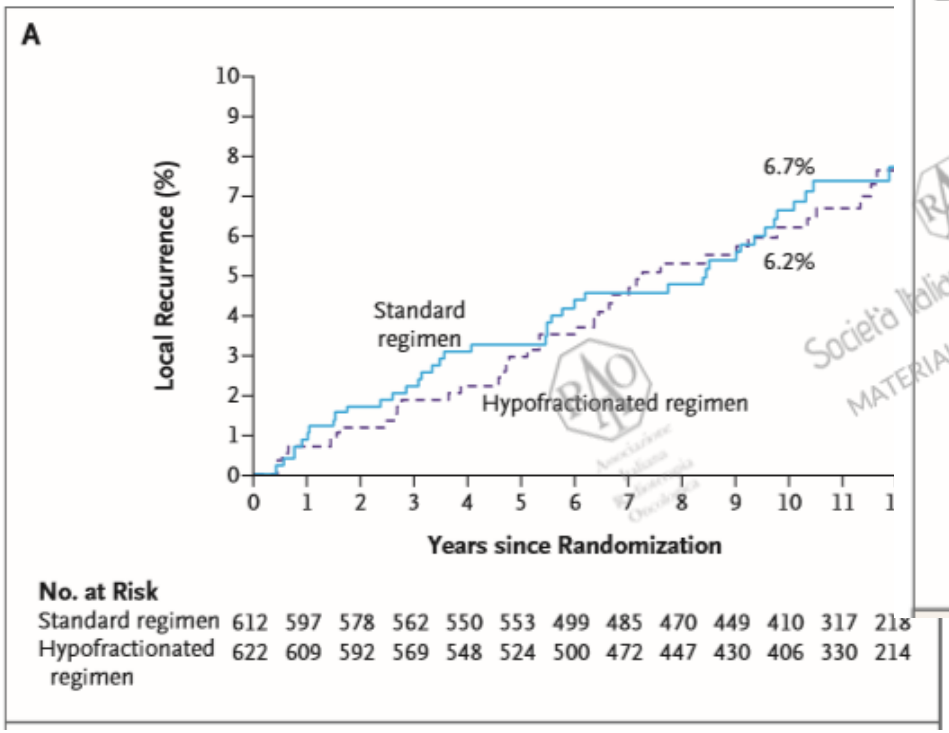
No difference in LR

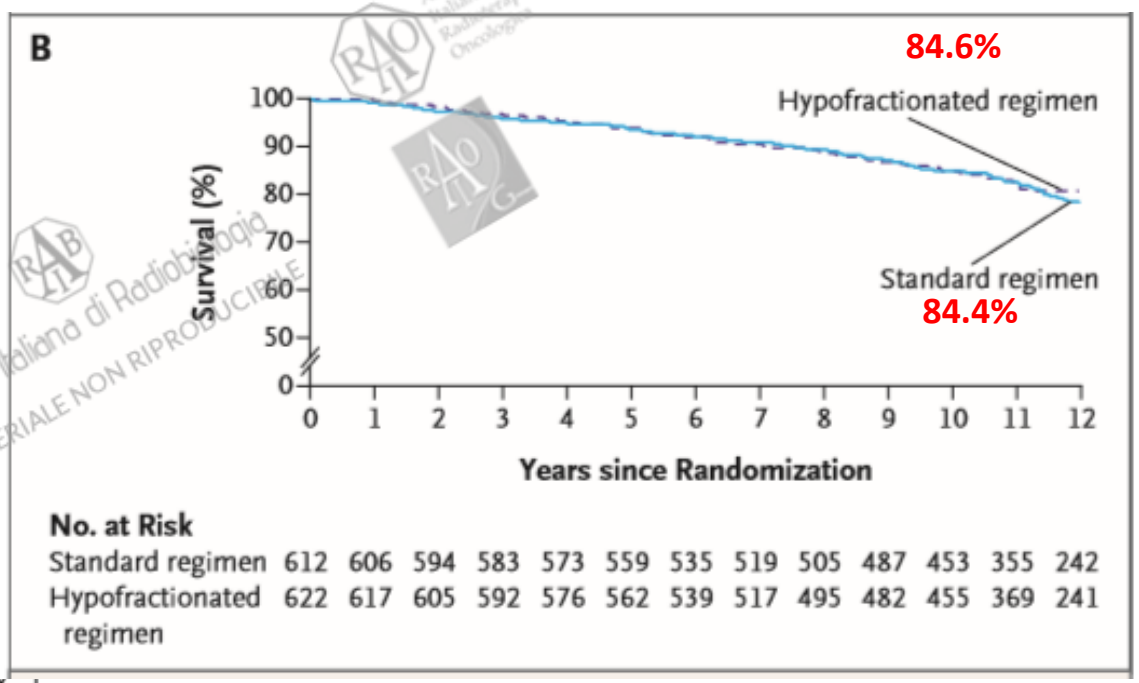
Lancet Oncol 2013; 14: 1086–94

Yarnold et al. The Breast 24 (2015): S108-113

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer





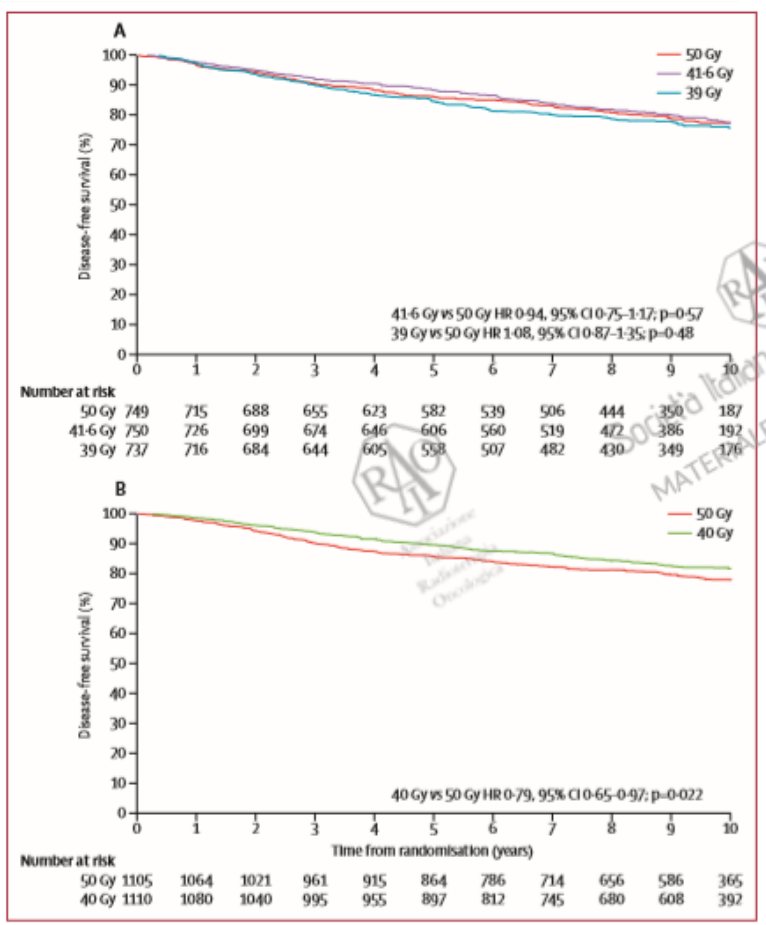
N Engl J Med 2010;362:513-20

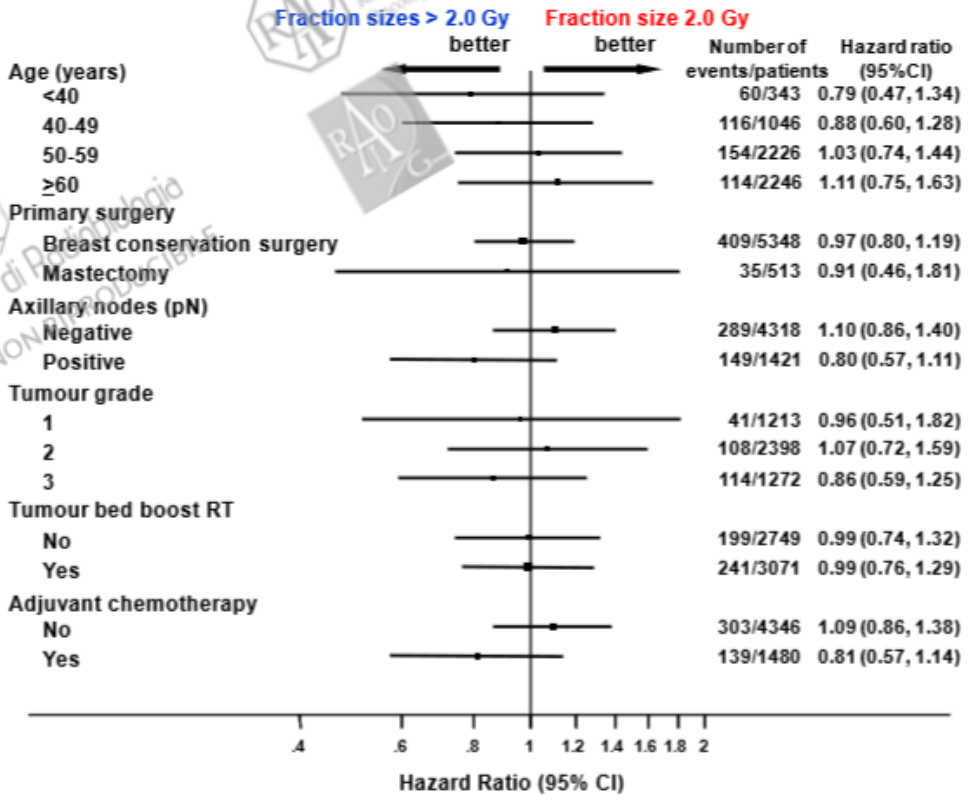
The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

START A

START B

DFS





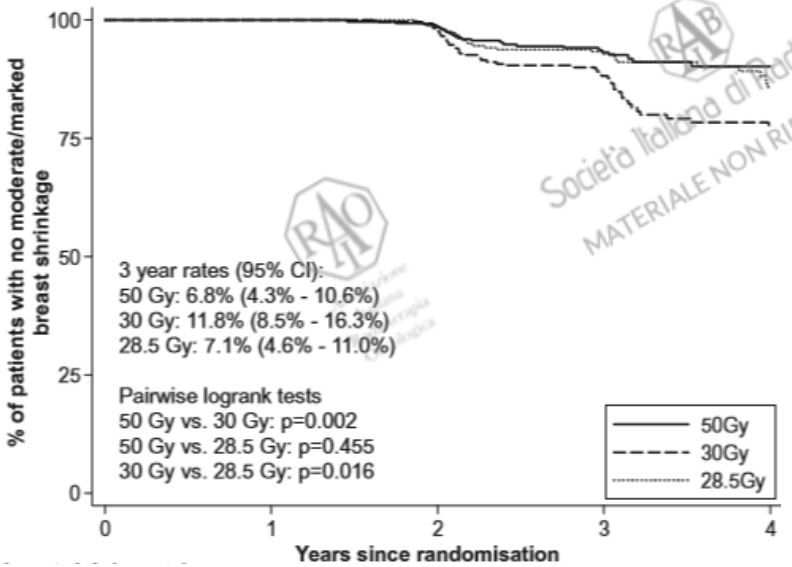
Lancet Oncol 2013; 14: 1086–94

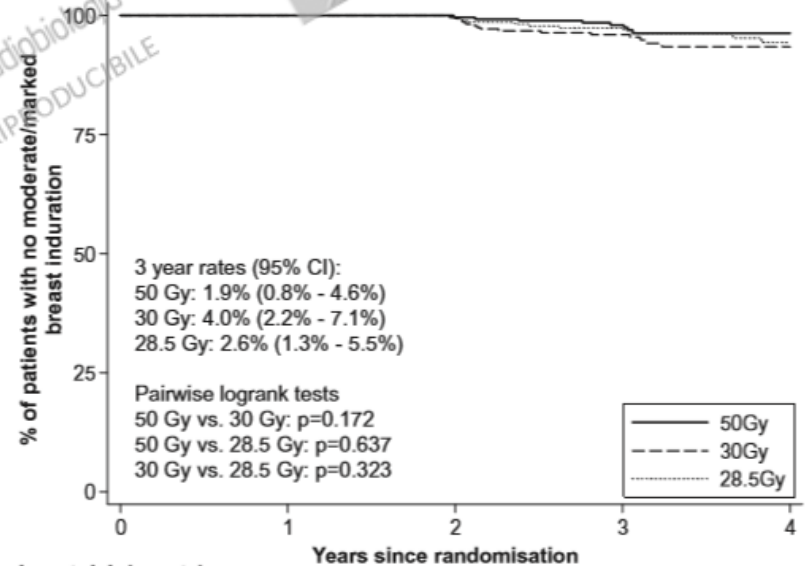
Phase III randomised trial

Radiotherapy and Oncology 100 (2011) 93–100

Conclusion: At 3 years median follow-up, 28.5 Gy in 5 fractions is comparable to 50 Gy in 25 fractions, and significantly milder than 30 Gy in 5 fractions, in terms of adverse effects in the breast.

The FAST Trialists group





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Quali pazienti (età? grading? alto rischio?...)?

HF-RT su N o dopo mastectomia?

Boost?

Tossicità?

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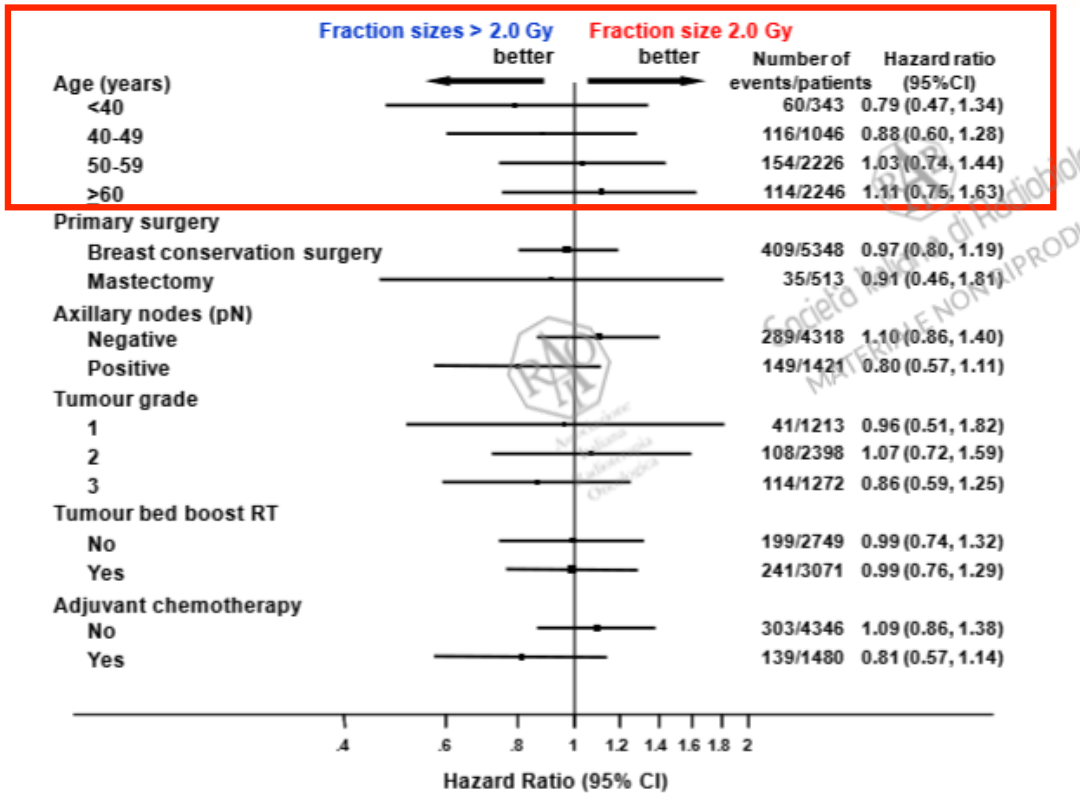
Age?

< 50 years → 20% to 35% risk of LR 10 years (***21-30% in trials of HF-WBI***)



This justifies the implication of hypofractionation for patients younger than 50 years.

N Engl J Med 2010;362:513-20

Lancet Oncol 2013; 14: 1086–94

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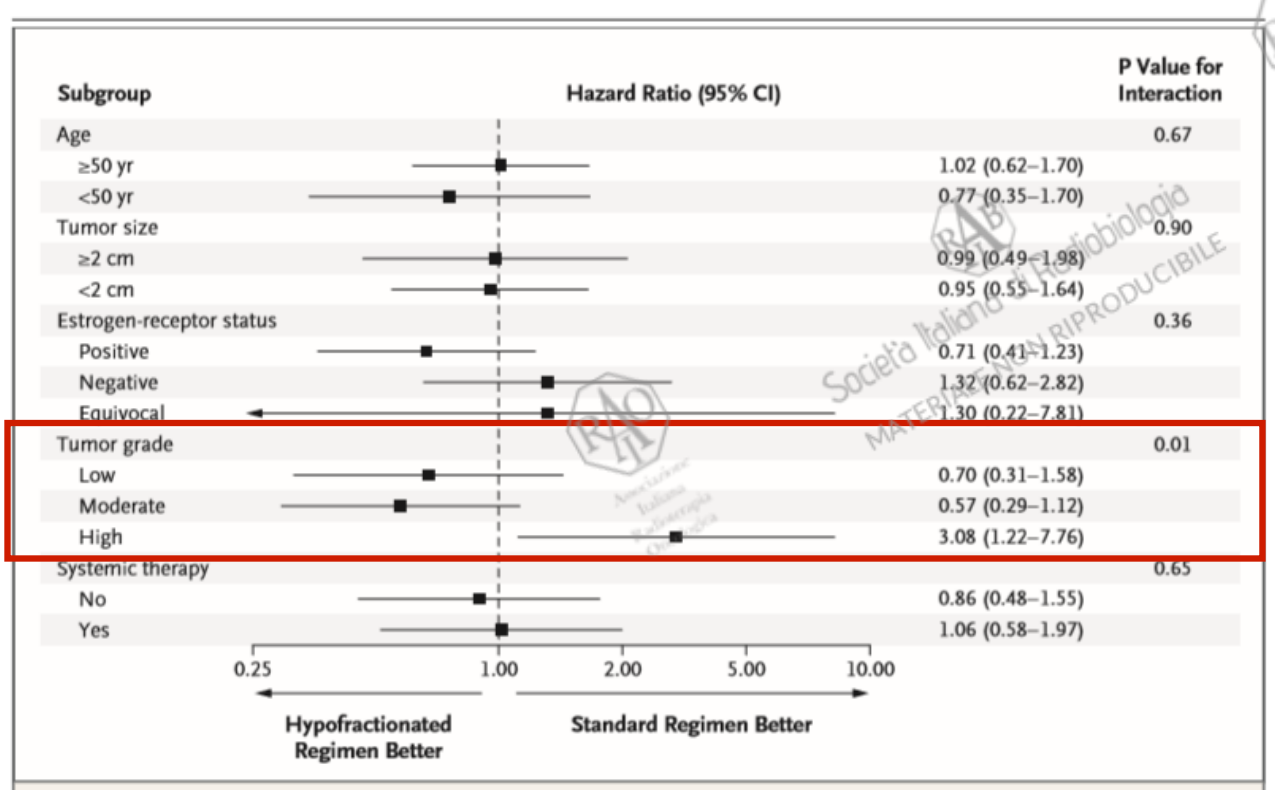
Grading ?



233 pz G3 (18.9%)

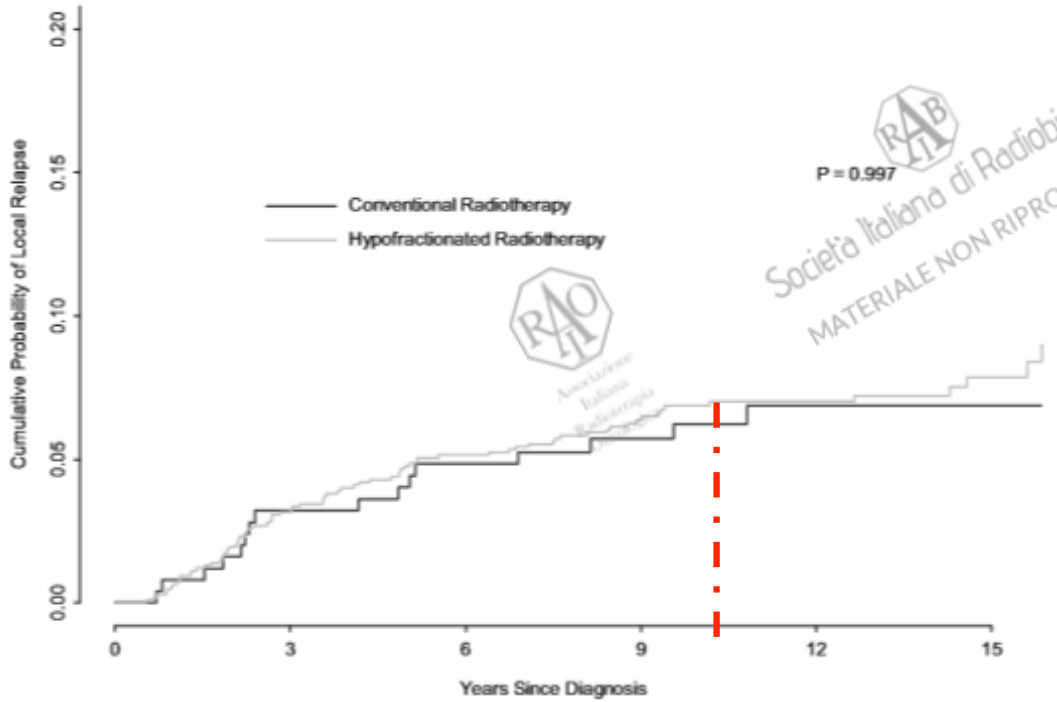
LR 10 y: 15.6% *vs* 4.7%

N Engl J Med 2010;362:513-20

CLINICAL INVESTIGATION Breast Cancer

THE IMPACT OF HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY ON LOCAL RELAPSE IN PATIENTS WITH GRADE 3 EARLY BREAST CANCER: A POPULATION-BASED COHORT STUDY

Christopher Herbert, F.R.C.R.,* Alan Nichol, F.R.C.P.C.,* Ivo Olivotto, F.R.C.P.C.,‡ Lorna Weir, F.R.C.P.C.,* Ryan Woods, M.Sc.,† Caroline Speers, B.A.,† Pauline Truong, F.R.C.P.C.,‡ and Scott Tyldesley, F.R.C.P.C.*



1335 pz (81.1% hypofr RT)
Median FUP: 12.1 years

	BCCA cohort	Canadian trial
< 50 years	40.1%	24.7%
T > 2 cm	32.8%	19.4%
ER+	42.8%	70.8%
Chemotherapy	62.2%	51.9%

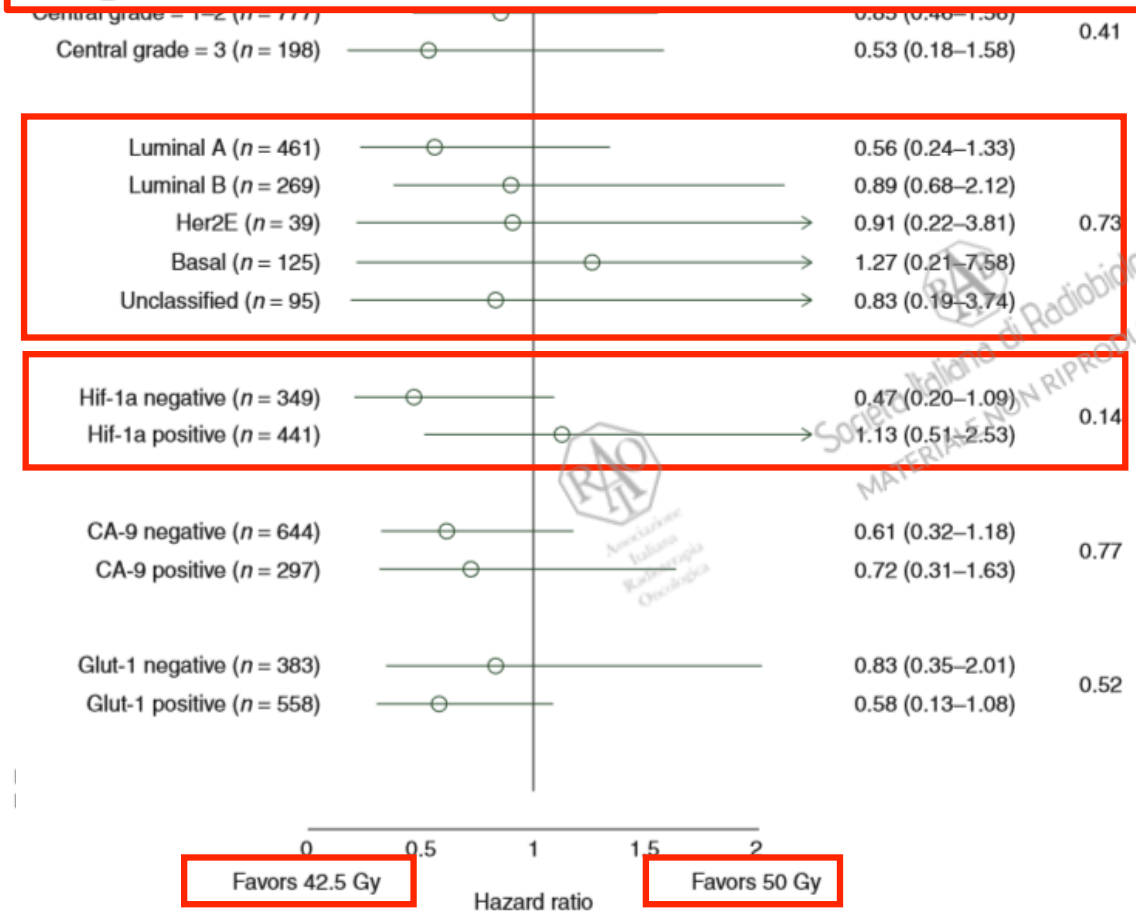
Herbert, IJROBP 2012 Vol 82, N.5: 2086-92

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

		Luminal A ($N = 461$)	Luminal B ($N = 269$)	HER2E[b] ($N = 39$)	Basal ($N = 125$)	Unclassified ($N = 95$)	*P*-value
Age	≥50 years	377 (81.8)	182 (67.7)	28 (71.8)	71 (56.8)	79 (83.2)	<0.001[c]
Size	>2 cm	62 (13.5)	68 (25.3)	13 (33.3)	42 (33.6)	14 (14.7)	<0.001[c]
Prior adjuvant systemic therapy	Tamoxifen	238 (51.6)	124 (46.1)	6 (15.4)	16 (12.8)	33 (34.7)	<0.001[c]
	Chemotherapy	12 (2.6)	22 (8.2)	12 (30.8)	64 (51.2)	11 (11.6)	
	None	211 (45.8)	123 (45.7)	21 (53.9)	45 (36.0)	51 (53.7)	
Grade (Nottingham)	I	125 (30.4)	29 (12.6)	1 (3.2)	3 (2.9)	20 (26.3)	<0.001[c]
	II	273 (66.4)	155 (67.4)	17 (54.8)	18 (17.5)	43 (56.6)	
	III	13 (3.2)	46 (20.0)	13 (41.9)	82 (79.6)	13 (17.1)	
Local Recurrence-free survival	*n* (%) Censored	439 (95.2)	248 (92.2)	31 (79.5)	120 (96.0)	88 (92.6)	<0.001[d]
	10-year (95% CI)	95.5 (93.0–97.2)	92.1 (87.8–95.0)	83.1 (66.2–92.1)	95.5 (89.5–98.1)	93.0 (85.0–96.8)	
Radiation treatment received	50 Gy	230 (49.9)	125 (46.5)	22 (56.4)	57 (45.6)	47 (49.5)	
HIF-1α	Positive[a]	170/373 (45.6)	145/238 (60.9)	22/32 (68.8)	93/110 (84.6)	11/37 (29.7)	<0.001[c]
CA-IX	Positive[a]	98/446 (22.0)	94/257 (36.6)	18/34 (52.9)	79/121 (65.3)	8/83 (9.6)	<0.001[c]
GLUT-1	Positive[a]	222/446 (49.8)	195/258 (75.6)	24/34 (70.6)	99/121 (81.8)	18/82 (22.0)	<0.001[c]

[a]Positive is defined as a score of ≥2 using the Allred criteria.
[b]HER2E; HER2-enriched subtype.
[c]χ^2 test.
[d]log-rank test.

Conclusions: In women enrolled in the HWBI trial following BCS tumor molecular subtype predicted LR. However tumor grade, molecular subtype and hypoxia did not predict response to hypofractionation suggesting that patients with node-negative breast tumors of all grades and molecular subtypes may be safely treated with hypofractionated RT regimens.



.uminal A	Luminal B	Her2E	Basal
4.5%	7.9%	16.9%	4.5%

Annals of Oncology25: 992–998, 2014

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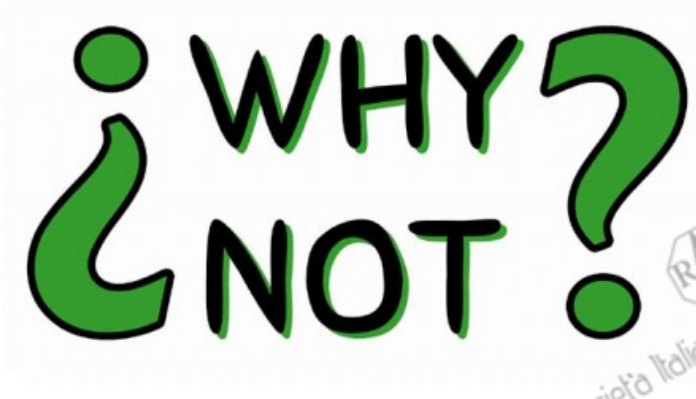

Regional node irradiation (RNI) ?

PMRT?

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Review

Radiotherapy and Oncology 110(2014): 39-44

Hypofractionated regional nodal irradiation for breast cancer: Examining the data and potential for future studies

Shahed N. Badiyan [a], Chirag Shah [b], Douglas Arthur [c], Atif J. Khan [d], Gary Freedman [e], Matthew M. Poppe [f], Frank A. Vicini [g,*]

Study	Type	Year	Patients	Fractionation	Follow-Up (mo)	Outcomes
Marsden [12]	Randomized, prospective	1986–1998	1,410 (14% chemo, 20% RNI)	42.9/13 v. 39/13 v. 50/25 (All in 5 weeks)	115	No data regarding RNI subset of patients
START A [7]	Randomized,	1998–2002	2,236 (36%	41.6/13 v.	61	No difference in chest wall appearance, chest
						fractionation PMRT
UZ Brussels [15]	Randomized,	2007–2011	70 (33% RNI)	50/25 v. 42/	28	Reduced skin changes and lung function with
						Grade 2 + edema 4.4%, Grade 2 + fibrosis, 7.1%, Grade 2 + chest wall pain 1.8%, No Grade 2 + plexopathy 4% CT changes in lung
Thailand [33]	Retrospective	2004–2006	215 (all PMRT; 67 conventional, 148 Hypofractionated)	50/25 v. 42.4–47.7.2.65	39	No difference in loco-regional control; no difference in chest wall appearance, fibrosis, appearance, plexopathy, lymphedema, cardiac, pulmonary, or rib fractures

NO WORSE TOXICITY

LIMITED DATA

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Hypofractionated irradiation of infra-supraclavicular lymph nodes after axillary dissection in patients with breast cancer post-conservative surgery: impact on late toxicity

Marina Guenzi[1], Gladys Blandino[1*], Maria Giuseppina Vidili[3], Deborah Aloi[1], Elena Configliacco[1], Elisa Verzanini[1], Elena Tornari[1], Francesca Cavagnetto[2] and Renzo Corvò[1]

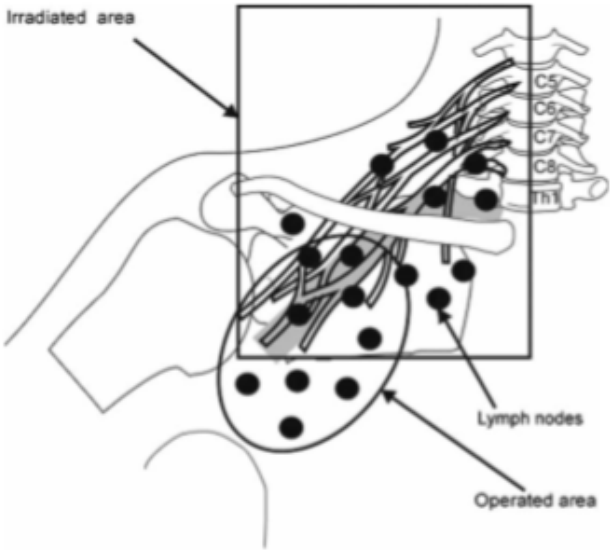
2007- 2012: 100 pz pT1- T4, pN1-3,Mx

WBRT+ RNI: 46 Gy in 20 fr 4 times a week
+additional weekly dose of 1,2 Gy to the lumpectomy area

Organ at risk	Normofractionation 2 Gy per fraction\5fr\week	Hypofractionated schedule 2,3 Gy per fraction\4 fr\week
LADCA	$V_{20Gy} = 0$ %	$V_{19Gy} = 0$ %
Heart	$V_{20Gy} = 10$ % V40Gy =5 %	$V_{19Gy} = 0$ %
Ipsilateral Lung	$V_{20Gy} = 25$ % (exclusive periclavicular LN)	$V_{19Gy} = 25$ % (exclusive periclavicular LN)
	$V_{20Gy} = 35$ % (inclusive periclavicular LN)	$V_{19Gy} = 35$ % (inclusive periclavicular LN)
Spinal cord	Max 45 Gy	Max 42 Gy

27 % lymphedema, but only 10 % seemed to be correlated to RT.
None of the patients showed a severe damage to the brachial plexus or symptomatic pneumonitis.

Guenzi et al. Radiation Oncology (2015) 10:177



Author	No. of patients	Median Follow-up [years]	Dose per fraction [Gy]	Total dose [Gy]	RIBP %	BED[1]
Stoll [16]	a)33	2.5	4.58	55	73	90
	b)84	2.5	4.25	51	15	80
	c)139	2.5	4.35	43.5	10	69
Johansson [18]	71	34	3.5[2]	57	63	78
Barr [20]	250	3	3.4	51	2.4	69
Powell [21]	a)338	5.5	3	45	5.9	56
	b)111	5.5	1.8	54	1	51
Basso-Ricci [22]	490	5	2[3]	60[3]	3.2	60[3]
Bajrovic [23]	140	8	2.6	52	14	59.8
Fairchild [26]	1142	8	2.5	40	<1	45
Livsey [31]	1665	5	2.27	34	no	36
Ragaz [9]	164	12.5	2.19	35	no	36.7
Olsen [32]	128	4	2.17	54.25	15	57
Delouche [24]	117	10	2	60	1.7	60
Fowble [14]	697	10	2	50	<1	50
Pierce [15]	724	6.5	2	50	0.4	50

Author	RIBP/ number of patients %	TD ≤50 Gy no CT %	TD ≤50 Gy with CT %	TD ≥50 Gy no CT %	TD ≥50 Gy with CT %
Pierce [15]	20/1117(1.8)	0.4	3.7; p =0.0002	3.2	7.9; p =NS
Olsen [32]	19/128*(15)	–	–	1.6	13; p =0.01

Galecki et al.Acta Oncologica, 2006; 45: 280-284

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Boost?

Tumor Bed Boost Integration during Whole Breast Radiotherapy: A Review of the Current Evidence

Pierfrancesco Franco[a] Domenico Cante[b] Piera Sciacero[b] Giuseppe Girelli[b]
Maria Rosa La Porta[b] Umberto Ricardi[a]

Study [ref.]	Country	Primary endpoint	Target population, n	Dose and fractionation (experimental arm)		
				whole breast	index quadrant	tumor bed
RTOG 1005 [40]	USA	in-breast relapse	2,300	40.05 Gy/15 fr (2.67 Gy daily)	/	48 Gy/15 fr (3.2 Gy daily)
IMPORT-HIGH [42]	UK	palpable induration	2,568	36 Gy/15 fr (2.4 Gy daily)	40.05 Gy/ 15 fr (2.67 Gy daily)	I: 48 Gy/15 fr (3.2 Gy daily) II: 53 Gy/15 fr (3.53 Gy daily)
IMRT MC-2 [43]	Germany	cosmetic outcome	502	50.4 Gy/28 fr (1.8 Gy daily)	/	64.4 Gy/28 fr (2.3 Gy daily)
UZB trial [44]	Belgium	pulmonary/cardiac function arm mobility and lymphedema	123	42 Gy/15 fr (2.8 Gy daily)	/	51/15 fr (3.4 Gy daily)

Hypofractionation and a concomitant tumor bed boost

Breast Care 2015;10:44–49

Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors

Patrizia Ciammella[1*], Ala Podgornii[1], Maria Galeandro[1], Renato Micera[1], Dafne Ramundo[1], Tamara Palmieri[1], Elisabetta Cagni[2] and Cinzia Iotti[1]

Table 8 Univariate and multivariate analysis predictive factors for late radiation induced subcutaneous toxicity

Variables	Univariate analysis	Multivariate analysis
	p value	*p* value [OR]
Chemotherapy	0.118	= 0.0184 [OR 2.5923 (1.1745 – 5.7217)]
Hypertension	0.705	0.731
Age	0.956	0.223
V > 100%	-	0.745
V > 104%	-	= 0.00864 [OR 0.07605 (0.01122 – 0.51517)]
V > 107%	-	= 0.02045 [OR 6.26889 (1.33829 – 29.36504)]
Boost V > 100%	-	0.728
Boost V > 104%	-	0.099
Boost V > 107%	-	0.585

Conclusion: These results confirm the feasibility and safety of the hypofractionated radiotherapy in patients with early breast cancer. In our population the boost administration was resulted to be a significant adverse prognostic factor for acute and late toxicity. Long-term follow up is need to confirm this finding.

Boost 9 Gy/3 Gy (55 pz)

Table 6 Frequency of any grade of late subcutaneous toxicity

RTOG Toxicity grade	Total patients N (%)
G0	136 (64%)
G1	72 (34%)
G2	3 (1.5%)
G3	1 (0.5%)

Radiation Oncology 2014, 9:97

Factors influencing acute and late toxicity in the era of adjuvant hypofractionated breast radiotherapy

M.C. De Santis [a,*], F. Bonfantini [b,1], F. Di Salvo [c,1], M. Dispinzieri [a], E. Mantero [a], F. Soncini [a], P. Baili [c], M. Sant [c], G. Bianchi [d], C. Maggi [d], S. Di Cosimo [d], R. Agresti [e], E. Pignoli [b], R. Valdagni [f], L. Lozza [a]

537 pz

42.4 Gy in 16 fraz (2.65 Gy fr)

+ boost (27%)

(for grade III, 10 Gy in 4 fr o 16 Gy in close or positive margins)

Median age: 74 yr

Chemotherapy: 22%

Median FUP: 32 months

	Acute	Late
Skin toxicity		
0	98 (18.3%)	535 (99.6%)
1	329 (61.3%)	2 (0.4)
2	105 (19.6%)	
3	5 (0.9%)	
Asthenia		
0	370 (68.9%)	535 (99.6%)
1	151 (28.1%)	1 (0.2%)
2	16 (2.3%)	1 (0.2%)
Edema		
0	442 (82.3%)	482 (89.7%)
1	88 (16.4%)	46 (8.6%)
2	7 (1.3%)	8 (1.5%)
3		1 (0.2%)
Fibrosis		
0	471 (87.7%)	446 (83.1%)
1	61 (11.4%)	68 (12.6%)
2	5 (0.9%)	22 (4.1%)
3		1 (0.2%)

The Breast 29 (2016): 90-95

Variables	n	Univariate analysis: Acute skin toxicity OR	Acute skin toxicity p-value[a]	Late fibrosis toxicity OR	Late fibrosis toxicity p-value[a]
Diabetes					
No	490 (91.3%)	1		1	
Yes	47 (8.7%)	0.9	0.61	**2.0**	**0.04**
Hypertension					
No	281 (52.3%)	1		1	
Yes	256 (47.7%)	1.2	0.31	0.9	0.76
Chemotherapy					
No	418 (77.8%)	1		1	
Yes	119 (22.2%)	1.5	0.08	**1.7**	**0.04**
Hormonotherapy					
Chemo and hormone therapy	85 (15.8%)	1.9	0.06	1.7	0.20
Breast volume (PTV)					
1°t (<553.1 cc)	149 (33%)	1		1	
2°t (553.1 – 806.9 cc)	151 (33.5%)	1.0	0.93	1.2	0.55
3°t (>806.9 cc)	151 (33.5%)	**1.6**	**0.05**	1.4	0.22
Breast PTV receiving a dose ≥44.52 Gy (105% of PTD)					
<Median value (92.5 cc)	220 (48.4%)	1		1	
>= Median value	235 (51.6%)	**2.0**	**<0.01**	**1.9**	**0.01**
Breast PTV receiving a dose ≥45.37 Gy (107% of PTD)					
<Median value (34.4 cc)	224 (48.7%)	1		1	
>= Median value	236 (51.3%)	**1.9**	**<0.01**	**2.0**	**<0.01**
Breast PTV receiving a dose ≥46.64 Gy (110% of PTD)					
<Median value (4.8 cc)	222 (48.3%)	1		1	
>= Median value	238 (51.7%)	**2.1**	**<0.01**	**1.6**	**0.04**
Boost administration					
No	393 (73.2%)	1		1	
Yes	144 (26.8%)	**2.5**	**<0.01**	**2.2**	**<0.01**
Boost volume					
<Median value (46.3)	63 (50.8%)	1		1	
>= Median value	61 (49.2%)	**2.1**	**0.04**	1.4	0.38

Conclusions: The results of our study, according to the large randomized trials, confirmed that hypo-fractionated whole breast irradiation is safe, and only the boost administration seems to be an important predictor for toxicity. Chemotherapy does not impact on acute and late skin toxicity.

Variables	n	Multivariate analysis: Acute skin toxicity OR	Acute skin toxicity p-value[a]	Late fibrosis toxicity OR	Late fibrosis toxicity p-value[a]
Diabetes					
1°t (<553.1 cc)	149 (33%)	1		1	
2°t (553.1 – 806.9 cc)	151 (33.5%)	0.9	0.67	1.2	0.65
3°t (>806.9 cc)	151 (33.5%)	1.3	0.40	1.2	0.53
Breast PTV receiving a dose ≥44.52 Gy (105% of PTD)					
<Median value (92.5 cc)	220 (48.4%)	1		1	
>= Median value	235 (51.6%)	1.3	0.47	0.9	0.86
Breast PTV receiving a dose ≥45.37 Gy (107% of PTD)					
<Median value (34.4 cc)	224 (48.7%)	1		1	
>= Median value	236 (51.3%)	0.7	0.38	2.1	0.21
Breast PTV receiving a dose ≥ 46.64 Gy (110% of PTD)					
<Median value (4.8 cc)	222 (48.3%)	1		1	
>= Median value	238 (51.7%)	1.7	0.10	0.6	0.35
Boost administration					
No	393 (73.2%)	1		1	
Yes	144 (26.8%)	**1.9**	**0.02**	1.5	0.24

The Breast 29 (2016): 90-95

Società Italiana di Radiobiologie

XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

Toxicity ?

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Table 2. Global Cosmetic Outcome, Assessed According to the EORTC Scale.*

Rating	Baseline			5 Yr			10 Yr		
	Standard Regimen (N=604)	Hypofractionated Regimen (N=616)	Absolute Difference (95% CI)	Standard Regimen (N=423)	Hypofractionated Regimen (N=448)	Absolute Difference (95% CI)	Standard Regimen (N=216)	Hypofractionated Regimen (N=235)	Absolute Difference (95% CI)
	percent of patients		*percentage points*	*percent of patients*		*percentage points*	*percent of patients*		*percentage points*
Excellent	46.3	46.8		34.3	36.4		27.8	30.6	
Good	36.3	37.0		44.9	41.5		43.5	39.2	
Fair	15.1	14.6		17.3	19.0		25.5	25.4	
Poor	2.3	1.6		3.5	3.1		3.2	4.8	
Excellent or good	82.6	83.8	−1.2 (−5.4 to 3.1)	79.2	77.9	1.3 (−4.2 to 6.7)	71.3	69.8	1.5 (−6.9 to 9.8)
Subcutaneous tissue									
0‡	61.4	66.8		45.3	48.1				
1	32.5	29.5		44.3	40.0				
2	5.2	3.8		6.8	9.4				
3	0.9	0.9		3.6	2.5				

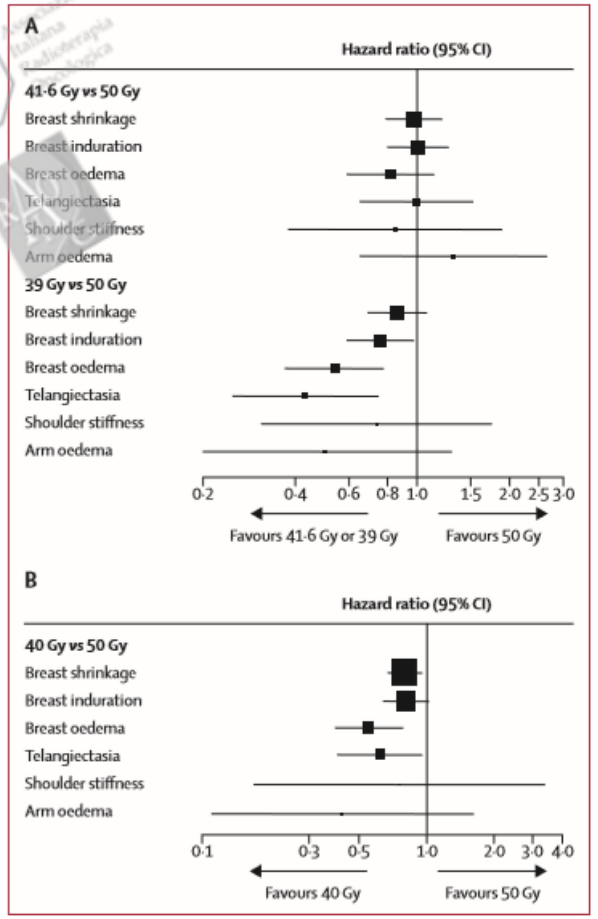
N Engl J Med 2010;362:513-20

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

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: **Incidence of other late adverse effects according to fractionation schedule**



Cardiac toxicity

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

Farmaci innovativi e ipofrazionamento

PALACONGRESSI DI RIMINI - 30 settembre, 1 - 2 ottobre 2016

Left-sided cases					Right-sided cases				
Variable	Statistic	CF-WBI (N = 485)	HF-WBI (N = 2221)	p-Value*	Variable	Statistic	CF-WBI (N = 455)	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%)	

5334 pz:

2221 pz HF-WBI

485 pz CF-WBI

SX

median FUP 14.2 years

Cause of death	Left-sided cases (N = 2706)				Right-sided cases (N = 2628)			
	CF-WBI	HF-WBI	p-Value (unadjusted)	p-Value (propensity score model)	CF-WBI	HF-WBI	p-Value (unadjusted)	p-Value (propensity score model)
Cardiac	4.2% (2.5, 6.5)	4.8% (3.9, 5.9)	0.74	0.45	3.47% (2.0, 5.6)	4.94% (4.0, 6.1)	0.21	0.15
Breast	16.2% (12.8, 19.9)	13.9% (12.5, 15.5)	0.28	0.16	13.37% (10.3, 16.9)	13.67% (12.2, 15.2)	0.49	0.25
Other	13.4% (10.2,	10.9% (9.5,	0.43	0.47	8.98%	11.10%	0.21	0.26

15-year cumulative mortality

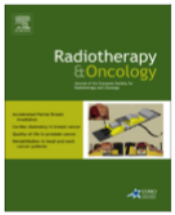
NO DIFFERENCE

N stage	0 nodes +ve	398 (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%)	

Radiotherapy and Oncology 113(2014): 73-78

Radiotherapy and Oncology 108 (2013) 203–208

Organ	Dose-volume	Treatment group		*p*-value
		Supine	Prone	
PTV_{optim}	Coverage (%)	92.7 ± 4.9	96.2 ± 2.2	**<0.001**
	Homogeneity	0.87 ± 0.04	0.90 ± 0.04	**<0.001**
	V_{105} (cc)	30.9 ± 40.4	8.9 ± 17.7	**<0.001**
	V_{107} (cc)	7.6 ± 12.6	0.9 ± 2.7	**<0.001**
Heart	D_{mean} (Gy)	2.0 ± 1.1	1.5 ± 0.6	0.08
	D_{max} (Gy)	12.1 ± 9.5	9.7 ± 6.5	0.25
	V_5 (%)	5.9 ± 5.5	3.8 ± 3.9	0.09
	V_{20} (%)	1.4 ± 2.3	0.7 ± 0.9	0.12
LAD	D_{mean} (Gy)	9.3 ± 6.5	5.4 ± 3.7	**0.007**
	D_{max} (Gy)	23.0 ± 11.7	19.5 ± 11.1	0.25
Ipsilateral lung	D_{mean} (Gy)	3.8 ± 1.1	1.1 ± 0.9	**<0.001**
	D_{max} (Gy)	26.6 ± 6.5	8.6 ± 8.9	**<0.001**
	V_5 (%)	16.9 ± 5.7	2.9 ± 3.7	**<0.001**
	V_{20} (%)	5.5 ± 3.3	0.9 ± 2.1	**<0.001**



Breast dose inhomogeneity	Total equivalent dose (Gy) if $\alpha/\beta = 3$ Gy, and you use fractions of …		
	2 Gy	4 Gy	6 Gy
100%	50.0	50.0	50.0
	↓		
105%	53.6	54.0	54.3 'triple trouble'
	→ 'double trouble'	→	

Dose inhomogeneity	% equivalent dose in 2.0 Gy fractions at different fraction sizes				
	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy
105%	107.1%	107.1%	108.0%	108.3%	108.5%
110%	114.4%	115.5%	116.3%	116.9%	117.3%
115%	121.9%	123.6%	124.9%	125.8%	126.5%

"Triple trouble"

the clinical consequences of high doses to small volumes are much less than high doses delivered to large volumes.

J. Yarnold et al. / The Breast 24 (2015) S108-S113
IJROBP 2011 vol 79; N1, pp 1-9

- Hypofractionation was also associated with **fewer normal tissue effects.**

- These **outcomes** were the same irrespective of age, tumour grade, stage, chemotherapy use, or use of tumour bed boost.

- Thus, the shorter regimen is safe and effective for most women with breast cancer, and **might be the preferred strategy.**

- Widespread use of a 3 week course of radiation would **reduce health-care costs**, whilst maintaining high treatment quality without compromising outcomes.

Hypofractionation for Breast Cancer: Lessons Learned From Our Neighbors to the North and Across the Pond

ONCOLOGY
Review Article | June 15, 2014 | Oncology Journal, Breast Cancer, Radiation Oncology
By Michael J. Eblan, MD, Noam A. VanderWalde, MD, Elaine M. Zeman, PhD, and Ellen Jones, MD, PhD

Adjuvant whole breast irradiation was established within the standard of care for breast-conserving therapy in the early 1980s, following the results of major randomized trials comparing mastectomy vs breast-conserving surgery and radiation. Since that time, techniques and treatment strategies have evolved, but one major thread that carries forward is the need to balance cost, efficacy, complications, and convenience. Fortunately, data from randomized trials conducted in Canada and Great Britain provide a solid framework for the consideration of hypofractionated radiation in the treatment of breast cancer. In this review we discuss the rationale and underlying radiobiologic concepts for hypofractionation, and review the clinical trials and American Society for Radiation Oncology (ASTRO) guidelines supporting this approach. We also review the practical considerations for treatment planning, including dosimetric criteria and how to approach treatment of the node-positive patient. In the current era of healthcare reform and cost awareness, thoughtful utilization of hypofractionation may offer considerable savings to individual patients and the healthcare system—without compromising clinical outcomes or quality of life.

Farmaci innovativi e ipofrazionamento
PALACONGRESSI DI RIMINI - 30 settembre, 1 - 2 ottobre 2016

16 fraz
25 fraz

x 100 pz

2500-1600 = 900

900:16 = **56**

World J Radiol 2010 June 28;2(6):197-202


Grazie
Società Italiana di Radiobiologia
MATERIALE NON RIPRODUCIBILE