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13 dicembre 2014

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Radioterapia delle stazioni linfonodali sovra-sottoclaveari con schema ipofrazionato nella patologia mammaria: esperienza mono-istituzionale.



Dott.ssa Gladys Blandino





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1 week

2 week

3 week

4 week

5 week



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|||||

50Gy

More time.....



....reduction accesses to the
radiotherapy centre

... optimize the workload of a department

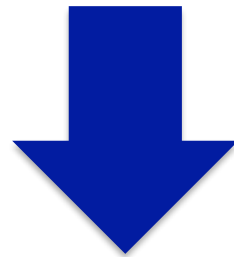




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**Conventional radiotherapy
schedula**



Hypofractionated schedula



The biologically effective dose (**BED**) for the innovative treatments was calculated using the linear-quadratic (LQ) model

$$BED = D \left(1 + \frac{d}{\alpha / \beta} \right)$$



$$\alpha/\beta_{\text{Tumor}} \approx 4\text{Gy}$$

Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues.

$$\alpha/\beta_{\text{Late healthy tissues responses}} \approx 3\text{Gy}$$

- Matthews J, 1989
- Steel G, 1987
- Cohen, 1952
- Douglas B, 1984
- Royal Marsden
- START A, 2008
- START B, 2008



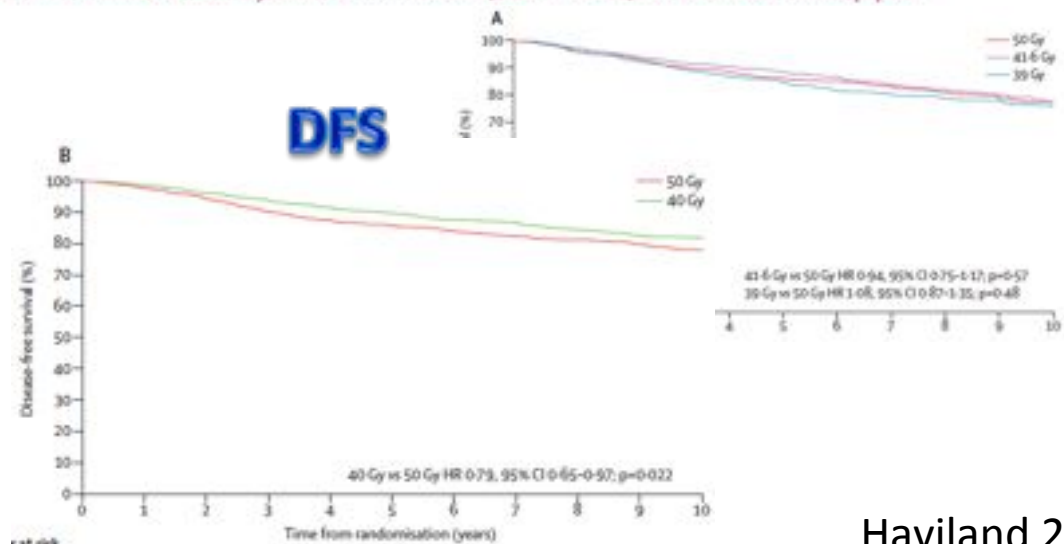
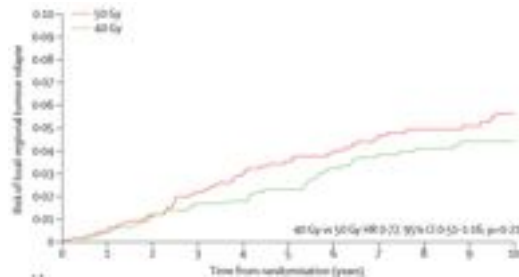
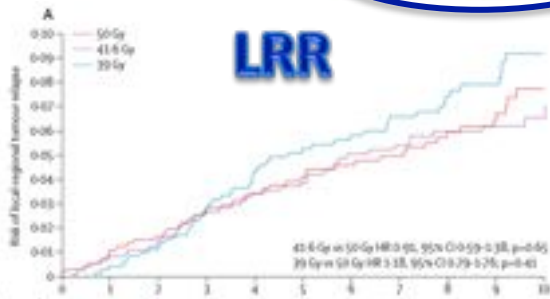
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The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

per Owens, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Iqbal Jazayeri, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the





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Haviland 2013 TOXICITY

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	165/616 (26.8%)	14.5% (11.5-17.2)	34.2% (29.8-39.2)	1.00	-
41.6 Gy	168/627 (26.8%)	17.8% (14.9-21.1)	31.4% (27.2-36.0)	0.98 (0.79-1.21)	0.83
39 Gy	149/617 (24.1%)	14.7% (12.0-18.0)	30.0% (25.7-34.8)	0.86 (0.69-1.08)	0.19
Breast induration (tumour bed)†					
50 Gy	143/616 (23.0%)	18.5% (15.6-21.9)	37.1% (33.3-41.3)	1.00	-
41.6 Gy	150/627 (23.9%)	18.9% (16.0-22.3)	28.2% (24.2-32.7)	1.01 (0.80-1.27)	0.95
39 Gy	110/617 (17.8%)	15.0% (12.3-18.3)	21.6% (18.1-25.7)	0.76 (0.59-0.98)	0.034
Telangiectasia					
50 Gy	43/730 (5.9%)	4.3% (3.0-6.1)	7.2% (5.2-9.8)	1.00	-
41.6 Gy	43/733 (5.9%)	4.9% (3.5-6.8)	7.1% (5.3-9.5)	1.00 (0.65-1.53)	0.99
39 Gy	18/733 (2.5%)	1.3% (0.6-2.5)	3.0% (1.8-5.0)	0.43 (0.25-0.75)	0.003
Breast oedema†					
50 Gy	28/616 (4.5%)	12.1% (9.7-15.0)	13.5% (10.9-16.6)	1.00	-
41.6 Gy	62/627 (9.9%)	9.2% (7.1-11.7)	11.8% (9.3-14.8)	0.82 (0.59-1.14)	0.24
39 Gy	43/617 (7.0%)	7.3% (5.5-9.7)	7.3% (5.5-9.7)	0.54 (0.32-0.93)	0.001
Shoulder stiffness					
50 Gy	14/117 (12.0%)	8.8% (4.7-16.4)	17.5% (10.2-29.1)	1.00	-
41.6 Gy	10/95 (10.5%)	7.1% (3.3-15.2)	14.8% (8.0-26.6)	0.85 (0.38-1.90)	0.69
39 Gy	8/92 (8.7%)	7.5% (3.4-16.0)	11.0% (5.6-21.0)	0.74 (0.31-1.76)	0.43
Arm oedema†					
50 Gy	15/117 (12.8%)	12.8% (7.6-21.2)	16.2% (9.9-26.2)	1.00	-
41.6 Gy	16/95 (16.8%)	11.9% (6.6-21.0)	22.5% (14.1-34.7)	1.31 (0.66-2.66)	0.45
39 Gy	6/92 (6.5%)	6.4% (2.7-14.7)	8.2% (3.7-17.6)	0.50 (0.20-1.30)	0.16
Other					
50 Gy	18/729 (2.5%)	1.3% (0.7-2.6)	3.4% (2.1-5.4)	1.00	-
41.6 Gy	20/733 (2.7%)	2.0% (1.2-3.4)	3.7% (2.3-6.1)	1.09 (0.58-2.06)	0.79
39 Gy	24/724 (3.3%)	2.3% (1.4-3.8)	3.9% (2.6-5.9)	1.37 (0.74-2.52)	0.31

*Assessed by Wald test, comparing each schedule with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 2: Physician-assessed normal tissue effects by fractionation schedule in START-A

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	256/1003 (25.5%)	15.8% (13.6-18.3)	31.2% (27.9-34.9)	1.00	-
40 Gy	221/1006 (22.0%)	11.4% (9.5-13.6)	26.2% (23.1-29.6)	0.80 (0.67-0.96)	0.015
Breast induration (tumour bed)†					
50 Gy	153/1003 (15.3%)	12.1% (10.2-14.4)	17.4% (14.9-20.3)	1.00	-
40 Gy	129/1006 (12.8%)	9.6% (7.9-11.6)	14.3% (12.1-16.9)	0.81 (0.64-1.03)	0.084
Telangiectasia					
50 Gy	52/1081 (4.8%)	3.8% (2.8-5.2)	5.8% (4.4-7.7)	1.00	-
40 Gy	34/1094 (3.1%)	1.8% (1.1-2.8)	4.2% (2.9-5.9)	0.62 (0.40-0.96)	0.032
Breast oedema†					
50 Gy	86/1003 (8.6%)	8.1% (6.6-10.1)	9.0% (7.3-11.0)	1.00	-
40 Gy	49/1006 (4.9%)	4.7% (3.5-6.2)	5.1% (3.9-6.7)	0.55 (0.39-0.79)	0.001
Shoulder stiffness†					
50 Gy	4/73 (5.5%)	2.9% (0.7-11.0)	8.2% (2.9-21.8)	1.00	-
40 Gy	3/81 (3.7%)	3.1% (0.8-11.9)	3.1% (0.8-11.9)	0.76 (0.17-3.39)	0.71
Arm oedema†					
50 Gy	7/73 (9.6%)	6.0% (2.3-15.3)	13.5% (6.4-27.0)	1.00	-
40 Gy	3/81 (3.7%)	2.8% (0.7-10.7)	4.7% (1.5-14.0)	0.42 (0.11-1.63)	0.21
Other					
50 Gy	7/1082 (0.7%)	5.6% (4.3-7.2)	8.1% (6.5-10.2)	1.00	-
40 Gy	53/1095 (4.8%)	3.3% (2.4-4.6)	6.4% (4.8-8.4)	0.65 (0.46-0.93)	0.018

*Assessed by Wald test compared with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 5: Physician-assessed normal tissue effects by fractionation schedule in START-B



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Review

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,*}



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Hypofractionated RNI studies.

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, prospective	1998-2002	2,236 (36% chemo, 15% PMRT, 14% RNI)	41.6/13 v. 39/13 v. 50/25	61	No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT
START B [7]	Randomized, prospective	1999-2001	2,215 (22% chemo, 8% PMRT, 7% RNI)	40/15 v. 50/25	72	No difference in chest wall appearance, chest pain/swelling, shoulder/arm function, and lymphedema compared with standard fractionation PMRT
UZ Brussels [15]	Randomized, prospective	2007-2011	70 (33% RNI)	50/25 v. 42/15	28	Reduced skin changes and lung function with hypofractionation at 2 years; no difference in fibrosis, lymphedema, or cardiac function.
Greece [32]	Prospective	2003-2010	112 (all PMRT, 73 RNI)	35/10	44	97% local control; no cases of pneumonitis. Acute toxicity- 23% Grade 2 + dermatitis in boost, 13% beyond field, No Grade 2 + chest pain, pneumonitis, edema, or erythema. Late toxicity- 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



Acta Oncologica, 2013; 52: 703–710

informa
healthcare

ORIGINAL ARTICLE: ACTA ONCOLOGICA JUBILEE ARTICLE

Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group

Mette H. Nielsen, 2013



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Table II. Constraints for organs at risk in adjuvant radiotherapy of early breast cancer.

Organ at risk	Normofractionation 2 Gy per fraction/ 5 fractions/week
LADCA	$V_{20\text{Gy}} = 0\%$
Heart	$V_{20\text{Gy}} = 10\%$, $V_{40\text{Gy}} = 5\%$
Ipsilateral lung	$V_{20\text{Gy}} = 25\%$ (exclusive periclavicular LN) $V_{20\text{Gy}} = 35\%$ (inclusive periclavicular LN) Mean dose < 18 Gy Max 45 Gy
Spinal cord	Max. 45 Gy
Plexus brachialis	Max. 54 Gy
Maximal dose of CTV	101% = 53.5 Gy
Maximal dose outside PTV	54 Gy

CTV, clinical target volume; LADCA, left anterior descending coronary artery; LN, lymph nodes; PTV, planning tumor volume.



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CRITICAL REVIEW

HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY FOR WOMEN WITH EARLY BREAST CANCER: MYTHS AND REALITIES

JOHN YARNOLD, F.R.C.R.,* SØREN M. BENTZEN, D.Sc.,† CHARLOTTE COLES, Ph.D.,‡
AND JOANNE HAVILAND, M.Sc.†



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Table 2. Randomised clinical trials testing fraction size in adjuvant external beam radiotherapy

Trial	Dose schedule (total dose/fraction no./treatment time (weeks) (fraction size))	5-year rate for		
		Any change in breast appearance (%)	Good/excellent breast cosmesis (%)	Local tumour relapse (%)
RMH/GOC 1986–1998	50.0/25/5.0 (2.0)	35.4	–	12.1
	39.0/13/5.0 (3.0)	27.4	–	14.8
	42.9/13/5.0 (3.3)	42.3	–	9.6
Ontario 1993–1996	50.0/25/5.0 (2.0)	–	79.2*	3.2 [†]
	42.5/16/3.2 (2.66)	–	77.9*	2.8 [†]
START A 1999–2002	50.0/25/5.0 (2.0)	42.9	–	3.2
	39.0/13/5.0 (3.0)	32.1	–	4.6
	41.6/13/5.0 (3.2)	43.6	–	3.2
START B 1999–2001	50.0/25/5.0 (2.0)	42.2	–	3.3
	40.0/15/3.0 (2.67)	36.5	–	2.0

Results of randomised clinical trials testing fraction size in adjuvant external beam radiotherapy to whole breast after local excision of early breast cancer. All trials used a control arm delivering 50 Gy in 25 fractions over 5 weeks.

* 71.3% and 69.8% at 10 years.

[†] 6.7% and 6.2% at 10 years.



NO CASES BRACHIAL PLEXOPHATY recorded in 112 patients given 40 Gy in 15 fractions in the START B trial at a median follow-up of 6.0 years

The regimen is equivalent to 47 Gy in 2.0-Gy fractions if the a/b value for brachial plexus is 2.0 Gy or to 49 Gy in 2.0-Gy fractions, if $a/b = 1.0$ Gy. If radiotherapy centers are confident that their technique is safe when prescribing 50 Gy in 25 fractions, there will be no excess risk after 40 Gy in 15 fractions by using the same treatment position, field arrangement, dosimetry, and reference point.



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Radiotherapy and Oncology 105 (2012) 273–282

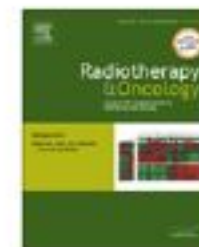


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Review

Radiation-induced neuropathy in cancer survivors [☆]

Sylvie Delanian ^{a,*}, Jean-Louis Lefaix ^b, Pierre-François Pradat ^c

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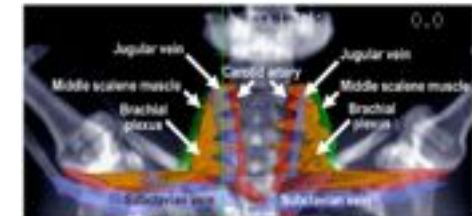
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Table 1
Chronic radiation-induced brachial plexopathy (RIBP) after shoulder girdle radiotherapy.

(1a) For breast cancer: incidence in large retrospective trials			
Series Breast cancer [Ref.]	Supraclavicular-axillary RT: total dose (size: dose/fraction) [reconstructed plexus dose]	RIBP incidence: number BP/total patients (%)	RIBP latency period (years) median
Stoll 66 [10] RT (1958-62) 2 series	(a) 63 Gy/12fr/25d (5.25 Gy/fr) Co [55 Gy] (b) 57.7 Gy/11fr (5.25 Gy/fr) [51] comorbidity: RM, compressive lymphoedema in 58%(a)25%(b)	(a) 24 BP/33 pts (73%) complete paralysis and sensory signs in 6 (b) 13 BP/84 pts (15%) complete paralysis in 1	(a) 14 mths (b) 19 mths 1.3 y (0.5-2.5 y)
Westling 72 [8] RT (1963-65)	44 Gy/11fr/23d (4 Gy/fr) isodose 130%/plexus. Axillary field with elevated arm [54] comorbidity: RM, lymphoedema	31 BP/71pts (44%) sensorimotor signs	3 y 1-4 y for 20 5-9 y for 8 10-22y for 6
Johanson 02 [12] RT (1963-68) 3 series	(a) 44 Gy/11fr/3wk (4 Gy/fr) [80] (b) 44 Gy/11fr (4 Gy/fr) Co-e' [82] (c) 45 Gy/15fr (3 Gy/fr) Co-e' [63] Coeq in smaller field sizes comorbidity: RM	(a) 45 BP/71 pts (63%) (b) 11 BP/23 pts (48%) (c) 8 BP/56 pts (14%) complete paralysis/150 pts: 30% at 5y, 50% at 15y, 67% at 30y	(a) 3y (1-19) (b) 4y (1-12) (c) 5y (1-18) (a) Incid 41%/y
Basso-Ricci 80 [31] RT 1965-72	RM 55 Gy/7fr/40d (>2 Gy/fr) [60]	16 BP/490 pts (3.2%) + others 26 BP drugs test (worse/vasodilators)	<2 y for 19 2-4 y for 10 >4 y for 13
Pierce 92 [45] RT (1968-85)	RT 2- or 3-field technique: 48-54 Gy/25fr (2-2.5 Gy/fr) [50] comorbidity: SM + CT	(a) 0 BP/507 pts 2-fields (b) 20 BP/1117 pt (0.2%) 3fields 16 acute + chronic and severe in 4	0.9 y (0.1'-6.4 y)
Rawlings 83 [32] RT 1967-74 RT 1967-74 RT 1969-80	45 Gy/18fr (2.5-3.3 Gy/fr) ± boost - exclusive RT [79] french technic - SM + RT [51] - BCS + RT [51] overlapping post field/supraclav	25 BP/1354 pts (1.8%) 9/245 (3.7%) for D > 60 Gy 11/650 (1.7%) 5/459 (1.1%) sensorimotor neurolysis in 6	0.5-10 y 3.5 y 4.5 y 3 y
Olsen 90 [29] RT (1977-82)	36.6 Gy/12fr/40d (3 Gy/fr): 2fr/wk comorbidity: SM (N dissection > 6), concomitant CT	(a) 28 BP/79 pts (35%) Mild in 13 Severe in 15	0.3'-5 y
Olsen 93 [30] RT (1982-90)	SM (11 nodes), sequential CT 50 Gy/25fr/38d (2 Gy/fr)	(b) 19 BP/161 pts (12%) Mild in 12 Severe in 7	Months?
Powell 90 [7] RT (1982-84) 2 series	SM or BCS + RT 3- or 4-field technique (80% isodose) pt turned (a) 51 Gy/15fr/6wk (3.4 Gy/fr) [46] (b) 60 Gy/30fr (2 Gy/fr) [54]	0 BP with 2 Gy/fr and 4-fields (a) 17 BP/338pts (5%) 13BP/3-ld (b) 1 BP/111pts (3-ld)	0.8-4 y incidence 1.8%/y
Bajrovic 04 [28] RT (1980-93)	SM or BCS, sequential CT 60 Gy/20fr (3 Gy/fr) Co with [52] 2.6 Gy/fr plexus	19 BP/ 140 pts (14%) severe in 2% at 5 y; 5.5% at 10 y; 12% at 15 y; 19% at 19 y	7.3y (2.5-18 y) incidence 2.9%/y 5 y:4%; 10 y:25%



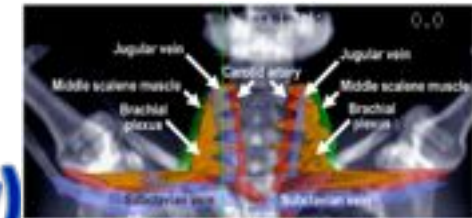
Delanian, 2012



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RIBP (Radiation-Induced Brachial Plexopathy)

- **1950s** with 60 Gy total dose axillary-supraclavicular delivered using 5 Gy/fr followed by 66% RIBP
- **1960s** with 45–50 Gy using 4 Gy/fr and patient removal between each RT field (overlapping) followed by 50% RIBP
- **1970s–1980s** with 45–50 Gy using 3 Gy/fr followed by 10–15% RIBP [then less than 5%
- **The incidence today** of RIBP is <1–2% in patients receiving usual plexus total doses <55 Gy



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OUR EXPERIENCE

- From 2007 to 2012
- 100 patients
- Conservative surgery – NDA
- T1-T4
- N1-N3



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CHARACTERISTICS

	N° PATIENTS	%
DCI	76	76%
LCI	16	16%
OTHER	8	8%

	N° PATIENTS	%
LUMINAL-A	59	59%
LUMINAL-B	24	24%
BASAL-LIKE	10	10%
HER-2 LIKE	7	7%



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CHARACTERISTICS

	N° PATIENTS	%
OT	82	82%
NEOADJUVANT CT	8	8%
ADJUVANT CT	81	81%
TRASTUZUMAB	21	21%

Chemotherapy scheme:

◆ Taxanes \ Anthracycline



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BREAST-LFN

1 week

2 week

3 week

4week

5 week



CC-BOOST

TOMOTHERAPY	19 PTS.	19%
LINEAR ACCELERATOR	81 PTS.	81%





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RESULTS

	N° PATIENTS	%
DIFFICULTY OF MOVEMENT	2	2%
PARESTHESIAS	3	3%
SWELLING	26	26%



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RESULTS

- ◆ Taxanes \ Anthracycline
- ◆ Surgery

	N° PATIENTS	%
DIFFICULTY OF MOVEMENT	2	2%
PARESTHESIAS	3	3%

➤ **NO BRACHIAL PLEXOPATHY**



RESULTS

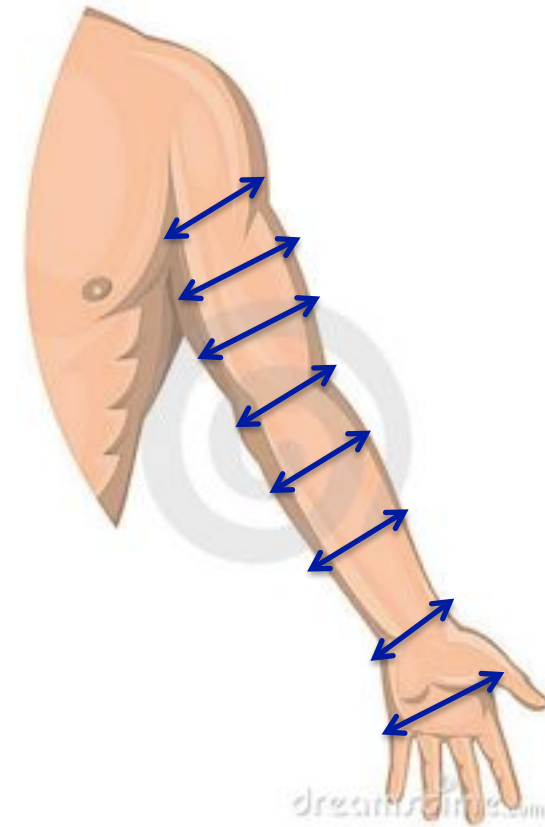
➤ LYMPHEDEMA

➤ 26 pts POST RT

➤ 3 pts PD

➤ 13pts PRE RT

N° pts	DT 5-9 cm	DT ≥10 cm
10 pts	3 pts	7 pts





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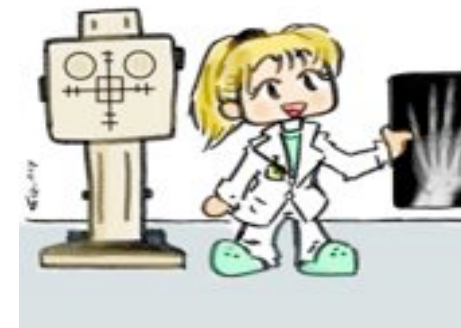
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CONCLUSIONS



- Median FU 47 months
- **No important toxicity**
(neuropathy and lymphedema)





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CONCLUSIONS



◆ Hypofractionated schedule → STANDARD

◆ Hypofractionated regional nodal irradiation

◆ Our experience



◆ Randomized study

Study	Type
Marsden [12]	Randomized, prospective
START A [7]	Randomized, prospective
START B [7]	Randomized, prospective
UZ Brussels [15]	Randomized, prospective
Greece [32]	Prospective
Thailand [33]	Retrospective



ASSOCIAZIONE ITALIANA RADIOTERAPIA ONCOLOGICA
Piemonte Valle d'Aosta Liguria



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13 dicembre 2014

V CONVEGNO
GRUPPO INTERREGIONALE AIRO



Grazie per l'attenzione