



Simposio Ricostruzione mammaria ed implicazioni radioterapiche

Volumi e dosi

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DICHIARAZIONE

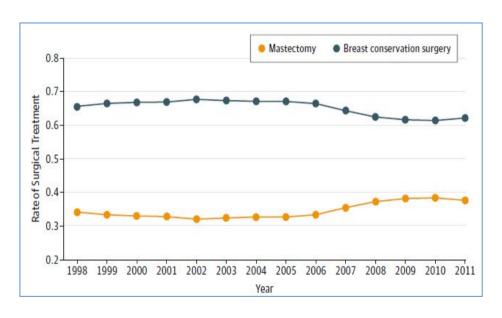
Relatore: Bruno Meduri

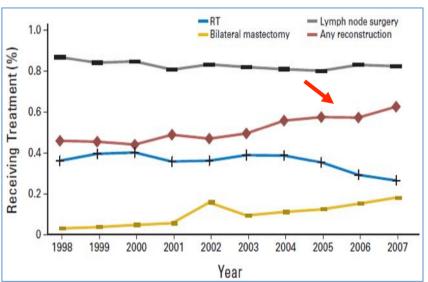
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- 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)

Post mastectomy radiotherapy (PMRT)

Sharp Rise in Mastectomy with reconstruction in Early-Stage Breast Cancer in USA

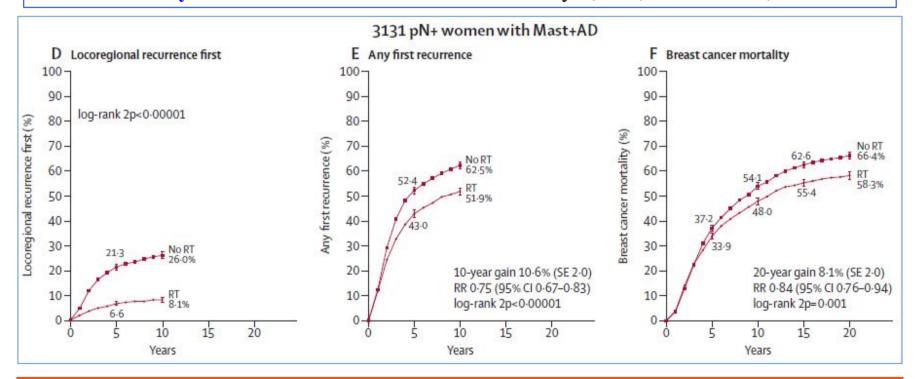




Post mastectomy radiotherapy (PMRT)

PMRT reduced in pN+ the

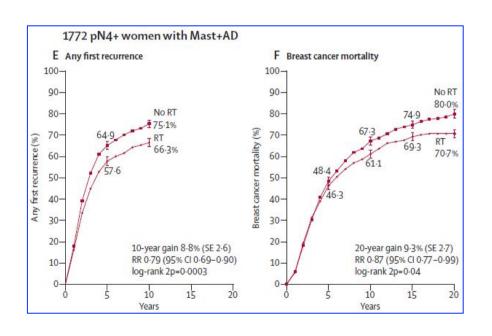
10-year risk of a recurrence of any type by 10,6% (62.5% vs 51.9%)
20-year risk of death from breast cancer by 8,1% (66.4% vs 58.3%)

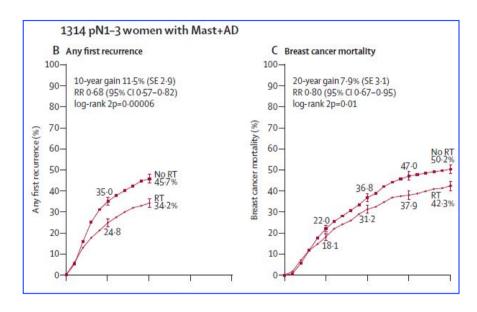


About **one breast cancer death** was avoided in the 20 years for every 1,5 recurrences of any type avoided during the first 10 years after radiotherapy

Post mastectomy radiotherapy (PMRT) Indications

Patients with high risk for LRR: pT3N+, pT4, $N+ \ge 4$





Patients with **intermediate risk for LRR**: pN+ 1-3

EBCTCG, *Lancet* **2014**; 383: 2127-35 Clarke M et al., *Lancet* **2005**; 366:2087-106 Ragaz J et al., *J Natl Cancer Inst* **2005**; 97:116-26 Overgaard M et al., *Lancet* **1999**; 353:1641-8

Post mastectomy radiotherapy (PMRT)

Target Volume

Chest wall

Axillary nodes

Supra/infraclavicular nodes

Internal mammary nodes

Chest wall

Axillary nodes

Supra/infraclavicular nodes

Internal mammary nodes

Chest wall

The most common site of locoregional relapse: 50-75%

	Median Interval	Isolate	d LRR	Total LRR	
Site	Service and the service of the servi	No.	%	No.	%
Chest wall	27	122	98	122	68
Supraclavicular	35	41	33	71	40
Axilla Infraclavicular Internal mammary Any site	With CHT	(doxorubicin-	based) and wit	thout RT	14 7 8 100

NOTE. Percentages represent fraction of LRRs including the specific site as a component of failure. Individual patients may have experienced more than one site of failure, so percentages do not total 100%.

Risk factors for LRR:

Grade, lymphovascular invasion, nodal ratio, T size, R+, age

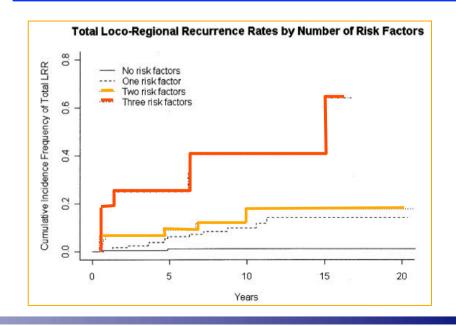
Chest wall in pN0 patients

% recurrences > 80%	Number of isolated locoregional recurrences (%)	Number of total locoregional recurrences (%)
Chest wall	28 (87.5%)	37 (80%)
Axilla	2 (6%)	3 (7%)
Supraclavicular region	1 (3%)	5 (11%)
IMC	1 (3%)	1 (2%)
Total	32 (100%)	46 (100%)

risk factors on LRR multivariate analysis:					
	Hazard ratio	p Value			
Margin (≥2 mm vs. <2 mm)	2.6	0.0210			
Menopausal status (pre vs post)	2.8	0.0051			
Size (>2 cm vs. \leq 2 cm)	3.8	0.0024			
Lymphovascular invasion	3.2	0.0088			
(positive vs. negative)					

LRR rate (10-year):

 $1.2\% \pm 0.9\%$ with 0 risk factors $10.0\% \pm 2.9\%$ with 1 risk factor $17.9\% \pm 7.5\%$ with 2 risk factors $40.6\% \pm 13.8\%$ with 3 risk factors



Chest wall

- High Risk for LRR: pT3N+, pT4, ≥4 pN+
- Intermediate Risk for LRR: 1-3 pN+ (depending on *risk factors*)
- Low Risk for LRR: pT2-3 N0 (depending on *risk factors*)



 $pT1-2\ N1M0 - pT2N0M0\ (if\ G3\ and/or\ LVI+) - pT3N0M0$ RT (CW \pm (SSC \pm IMN) VS No RT

Chest wall

Axillary nodes (I-II)

Supra/infraclavicular nodes

Internal mammary nodes

Axillary nodes

Absolute risk of recurrence after complete dissection of level I and II: <5%

Risk factor	55 m 2 m	Local	Axillary	Supraclavicular
	No. (%) of patients	percent (SE)	percent (SE)	percent (SE)
	Parens	(04)	(01)	(CALI)
Age, years	040 (10)		E 1 (0 E)	C 2 (0 0)
<40	949 (12)	16.1 (1.2)	5.1 (0.7)	6.3 (0.8)
40-49	2607 (32)	10.5 (0.6)	2.7 (0.3)	6.1 (0.5)
50-59	2452 (30)	9.6 (0.6)	2.4 (0.3)	6.3 (0.5)
≥60	2098 (26)	10.8 (0.7)	2.5 (0.3)	3.5 (0.4)
Nodes involved				
None	2555 (32)	6.8 (0.5)	1.3 (0.2)	2.2 (0.3)
1-3	3260 (40)	10.3 (0.5)	2.6 (0.3)	4.8 (0.4)
4-10	1744 (22)	15.4 (0.9)	4.9 (0.5)	8.8 (0.7)
≥11	547 (7)	19.9 (1.7)	4.9 (0.9)	14.8 (1.5)
Tumor size, cm				
≤2	3200 (39)	8.7 (0.5)	2.4 (0.3)	3.5 (0.3)
>2	4623 (57)	12.4 (0.5)	3.0 (0.3)	7.0 (0.4)
Unknown	283 (3)	12.9 (2.1)	5.2 (1.4)	3.8 (1.2)
Tumor grade			5 (1 of 10 and 1	11/14/06/04/04
1	1126 (14)	8.2 (0.8)	1.3 (0.4)	2.0 (0.4)
2	3520 (43)	10.7 (0.5)	2.6 (0.3)	4.3 (0.3)
3	3036 (37)	12.3 (0.6)	3.5 (0.3)	8.4 (0.5)
Unknown	424 (5)	11.1 (1.6)	3.8 (0.9)	4.5 (1.0)

Risk factor		Local	Axillary	Supraclavicular
0.000	No. (%) of	percent	percent	percent
	patients	(SE)	(SE)	(SE)
Peritumoral ves	sel invasion			
No	3823 (47)	8.6 (0.5)	2.0 (0.2)	3.8 (0.3)
Yes	2754 (34)	14.1 (0.7)	3.8 (0.4)	7.5 (0.5)
Unknown	1529 (19)	11.3 (0.8)	3.3 (0.5)	6.2 (0.6)
Nodes uninvolve	ed		5. Meses ravi	100000000000000000000000000000000000000
0-7	1925 (24)	15.1 (0.8)	5.2 (0.5)	9.3 (0.7)
8-11	1953 (24)	11.4 (0.7)	2.9 (0.4)	5.6 (0.5)
12-16	2126 (26)	9.8 (0.7)	2.2 (0.3)	4.3 (0.4)
≥17	2102 (26)	7.9 (0.6)	1.3 (0.2)	3.2 (0.4)
Nodes examined	i		alexander of the later	
≤10	1940 (24)	12.5 (0.8)	3.8 (0.4)	5.7 (0.5)
11-14	2076 (26)	9.4 (0.6)	3.5 (0.4)	6.0 (0.5)
15-19	2053 (25)	11.7 (0.7)	2.2 (0.3)	5.3 (0.5)
≥20	2037 (25)	10.3 (0.7)	2.0 (0.3)	5.1 (0.5)
Estrogen recepto	or status			
Negative	2383 (29)	10.6 (0.6)	3.1 (0.4)	7.7 (0.5)
Positive	4760 (59)	11.3 (0.5)	2.5 (0.2)	4.4 (0.3)
Unknown	963 (12)	10.0 (1.0)	3.6 (0.6)	5.5 (0.7)

Axillary nodes



Chest wall

Axillary nodes

Supra/infraclavicular nodes (III)

Internal mammary nodes

Supra/infraclavicular nodes (III)

20%-40% of all locoregional relapses (absolute risk 5-15%)

Characteristic	SCV/ICV	p value	
T stage			
TI	7% (20/337)	NS	
T2	10% (40/510)		
T3	7% (7/102)		
TX	9% (8/78)		
Tumor size			
≤1.0 cm	2% (1/45)	NS	
1.1-2.0 cm	7% (18/270)		
2.1-3.0 cm	8% (19/270)		
3.1-4.0 cm	15% (18/160)		
4.1-5.0 cm	8% (4/69)		
>5.0 cm	7% (7/103)		
Unknown	8% (10/105)		
No. involved nodes			
0	5% (3/142)	< 0.0001	
1-3	5% (20/465)		
4-9	15% (34/263)		
≥10	15% (20/157)		
No. nodes examined	190. 200.000.00.000		
<10	8% (6/113)	NS	
≥10	8% (71/018)		
LVSI		0.0008	
Absent	6.1% (35/644)		
Present	12.2% (39/364)		
Percentage nodes	50000000	200000	
≤20%	5% (21/453)	< 0.0001	
>20%	15% (52/424)		
Size of largest node	12 19/10/2 (19/10)	1920523	
≤1 cm	5% (7/148)	NS	
1.1-2 cm	8% (19/222)		
2.1–3 cm	11% (12/126)		
>3 cm	13% (6/58)		
Unknown	8% (33/477)		
Extranodal extension*	1 200 - 100 - 100 - 100	Service of the service of	
None	6% (43/711)	0.0012	
Present, NOS, or focal	11% (13/151)		
Gross	19% (20/142)		

In multivariate analysis:

lymphovascular invasion (HR 1.89; p 0.007 percentage of positive nodes (HR 1.01; p 0.0017)

For T1/T2 and pN+1-3:

Only *n. of N*+ predicted for increased failure (10- year recurrence with 3 N+ vs 2N+: 10% vs. 2%, p 0.004)

No statistically significant difference:

>20% involved axillary lymph nodes (9% vs. 4%, p 0.15)

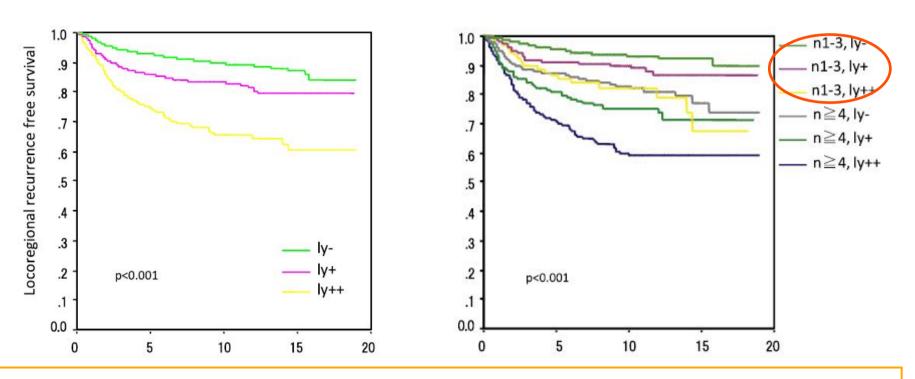
ECE (11% vs. 4%, p 0.21)

largest axillary node 2 cm (6% vs. 4%, p 0.26)

LVI (4% vs. 5%, *p* 0.65)

4 factors: 40%; 3 factors: 9%; 2 factors, 6%; p 0.001.

Supra/infraclavicular nodes in pN+ 1-3



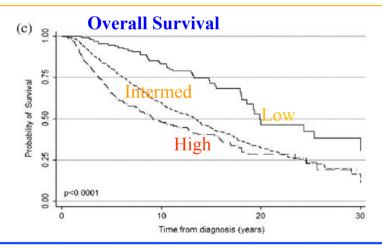
Ly++ level was associated with a *very high LRR*

Ly++ subgroup of N1-3 patients showing a higher LRR than the ly- subgroups of N4

Supra/infraclavicular nodes in pN+ 1-3

In multivariate analysis: *n. of N*+ (1 N+ vs 2 N+ [HR = 1.9] and 3 N+ [HR = 3.1], p < 0.001) and *grade* (G1: HR = 1, G2: HR = 12.2, G3, HR = 20.8 [p < 0.001])

	2	Gı	rade	
No. LNs	- 10	1	2	3
1	5 y	1.4	4.9	6.5
	10 y	1.4	8.9	8.9
2	5 y	0	7.6	12.1
	10 y	0	11.8	19.4
3	5 y	0	10.9	21.1
	10 y	0	14.8	29.6



Risk group

	G1	G2	G3
1 N	Low	Interm	Interm
2 N	Low	Interm	High
3 N	Low	High	High

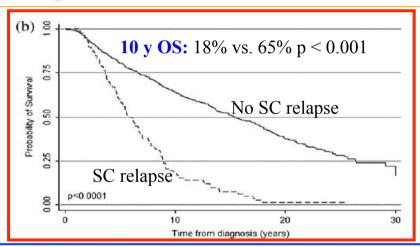
Table 4b.	5- and	10-year	SCFR	rate	and	hazard	ratios
	accordi	ng to the	e three	risk*	gro	oups	

Risk Group	Number (%)	5-y SCFR (%)	10-y SCFR (%)	HR (95% CI)	p Value
Low	131 (14)	0.8	0.8	1.0	< 0.001
Intermediate	580 (60)	6.0	9.6	13.5 (1.9-97.9)	
High	252 (26)	14.6	21.0	30.3 (4.2-220.3)	

Supra/infraclavicular nodes in pN+ 1-3

In multivariate analysis: *n. of N*+ (1 N+ vs 2 N+ [HR = 1.9] and 3 N+ [HR = 3.1], p < 0.001) and *grade* (G1: HR = 1, G2: HR = 12.2, G3, HR = 20.8 [p < 0.001])

	2	Gı	rade	
No. LNs	10	1	2	3
1	5 y	1.4	4.9	6.5
	10 y	1.4	8.9	8.9
2	5 y	0	7.6	12.1
	10 y	0	11.8	19.4
3	5 y	0	10.9	21.1
	10 y	0	14.8	29.6



Risk group

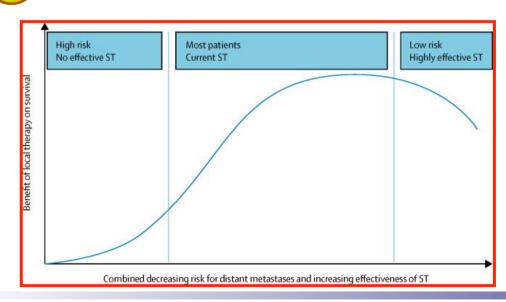
	G1	G2	G3
1 N	Low	Interm	Interm
2 N	Low	Interm	High
3 N	Low	High	High

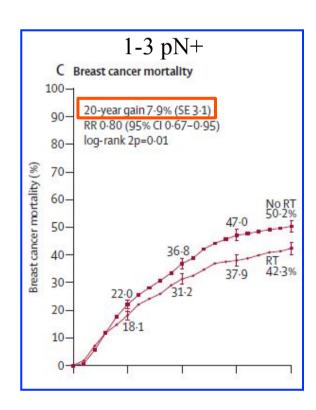
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Intermediate	580 (60)	6.0	9.6	13.5 (1.9-97.9)	
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Supra/infraclavicular nodes

- High Risk for LRR: pT3N+, pT4, ≥4 pN+
- **Intermediate Risk for LRR:** 1-3 pN+ (.. *risk factors*..)





Chest wall

Axillary nodes

Supra/infraclavicular nodes

Internal mammary nodes

Internal mammary nodes

Retrospective studies have shown that recurrence in the IMNs is rare (<5%)

	Table 2. IMN Invol	vement Based	on Primary T	umor Location	and Axillary S	tatus in Surgic	al Series		
		IMN-Positive Rate Among Ax-Positive Patients (%)				IMN-Positive Rate Among Ax-Negative Patients (%)			e Patients
Study	No. of Patients	Overall	Medial	Central	Lateral	Overall	Medial	Central	Lateral
Handley ²¹	1,000	40	50	46	22	11	12	7	4
Donegan ¹⁷	113	34	55	29	31	6	12	0	4
Caceres ²⁰	500	28	44	31	18	6	8	0	6
Urban and Marjani ²⁴ *	725	52	65	48	42	16	20	12	13
Livingston and Arlen ^{23*}	583	32	59	46	23	8	14	8	5
Huang et al ²⁵	1,679	28	32	36	24	4	7	2	3

Multiple series of surgical IMN evaluation were reported that consistently identified *medial tumors* and *positive axillary nodes* to be strongly associated with a **higher rate of IMN** +

Internal mammary nodes

A significant proportion (13%-37%) of patients have **primary IMN drainage** and that *medial tumors* are more likely than lateral tumors to drain to the IMN chain

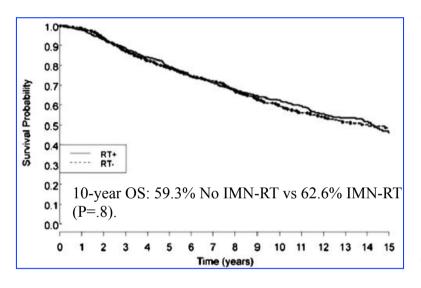
		Table	e 4. Lymphoso	cintigraphy Ide	ntification of II	M SN	
		% of	Patients With	n IM SN Visua	lized*		
Study	No. of Patients	Overall	Medial	Central	Lateral	IM SN Only (%)	IM SN Biopsy-Positive Rate (%)
Shahar et al ⁴⁹	297	21	25	28	16	1	<u>—</u>
Madsen et al ³⁶	506	22	42	18	14	1	24
Carcoforo et al ⁴⁵	741	13	20	13	5	1 	15
Byrd et al ⁴⁸	220	17	20	29	15	1	<u>—</u>
Estourgie et al ⁴⁴	700	21	34	23	14	2	13
van der Ent et al ⁴⁷	256	25	39†	8	16	0	27
Lamonica et al ⁴⁶	132	13	18	14	11	4	
Park et al ³⁸	83‡	17	28	17	13		
Paganelli et al ⁴¹	200‡	37	63	W	10	8	8

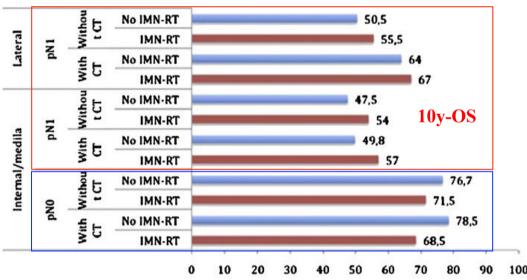
Up to 8% of patients had only IM sentinel nodes (not axillary sentinel nodes)

Mismatch low rate recurrence: seed and soil phenomenon ... recurrences less likely than other sites to be detected as *the first site of recurrence* (CT vs PET).

Internal mammary nodes

Patients (1407) pN+ or central/medial tumors with or without pN+. RT CW/SCN \pm IMN



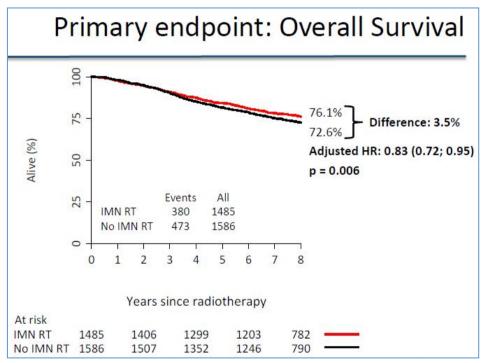


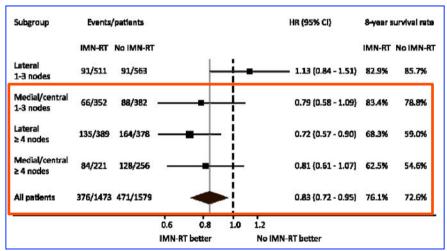
Not show a significant difference in OS according to the use or not of IMN-RT

It was designed to demonstrate a 10% benefit in overall survival → underpowered In **subgroups** with a particular high risk of IM nodes involvement a slight but not significant difference was observed

Internal mammary nodes

Patients (3072) with operable unilateral BC with macrometastases to one or more axillary LNs, prospectively allocated to adjuvant RT +/- IMN-RT depending on BC laterality



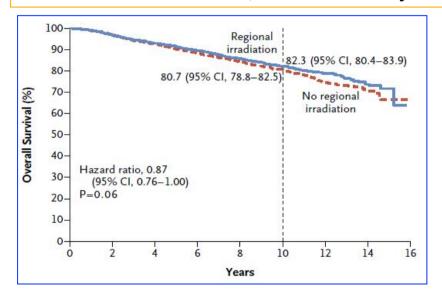


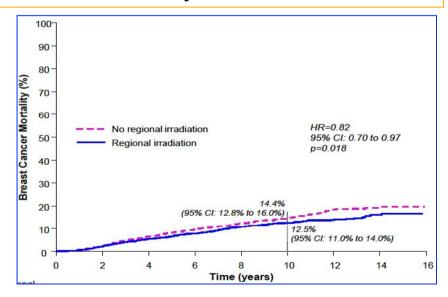
Overall survival improved with IMN-RT

Benefit increased with increasing number of N+ and medial or central tumor location

IMN: EORTC 22922

Patients (4004) with centrally or medially located primary tumor, *irrespective of axillary involvement*, or an externally located tumor with axillary involvement





Regional nodal irradiation was beneficial to women with early stage BC It improved the rates of DFS, DMFS and reduced the rate of death from BC Side effects were modest. Rate of death from causes \neq BC not increased FUP for a median of 20 years is ongoing

Internal mammary nodes



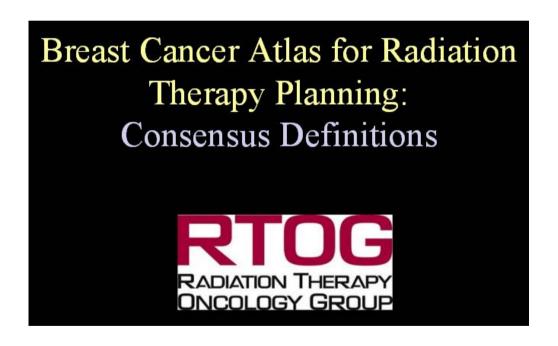
pN+ and centrally or medially located primary tumor (depending on *risk factors*)

	MA-20 [58]	EORTC [40]	Meta-analysis [6]
Design	WBI + IM + MS + Ax level III vs. WBI alone	WBI/CWI + IM + MS vs. WBI/ CWI alone	
n	1832	4004	Total 5836
OAS	HR 0.76	HR 0.87	HR 0.85
	(95% CI 0.75–0.96)	(95% CI 0.76–1.00)	(95% Cl 0.75–0.96)
	p=0.07	p=0.056	p=0.011
DFS	HR 0.67	HR 0.89	HR 0.85
	(95% CI 0.52–0.87)	(95% CI 0.80–1.00)	(95% Cl 0.77–0.94)
	p=0.003	p=0.044	p=0.002
MFS	HR 0.64	HR 0.86	HR 0.82
	(95% CI 0.47–0.85)	(95% CI 0.73–0.92)	(95% Cl 0.73–0.92)
	p=0.02	p=0.02	p=0.001

Comments and conclusions of the DEGRO panel

Medial tumor location should regain relevance among decision criteria for IMN-RT as part of RNI.

Contouring





Associazione Italiana di Radioterapia Oncologica Gruppo di lavoro AIRO per la Patologia Mammaria

La Radioterapia dei Tumori della Mammella

Indicazioni e Criteri Guida

Contouring

Loco-regional conformal radiotherapy of the breast: delineation of the regional lymph node clinical target volumes in treatment position

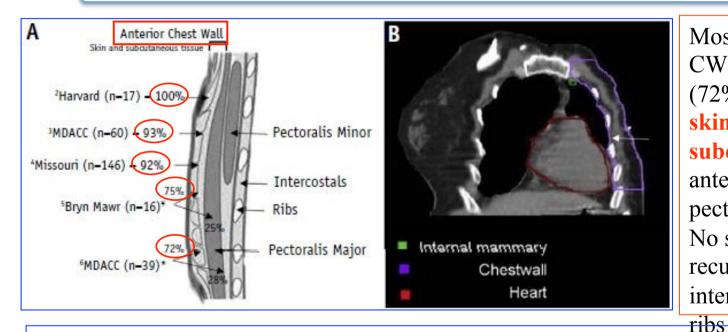
Ivessa M. Dijkema^{a,*}, Pieter Hofman^a, Cornelis P.J. Raaijmakers^a, Jan J. Lagendijk^a, Jan J. Battermann^a, Berend Hillen^b

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer



Birgitte V. Offersen ^{a,*}, Liesbeth J. Boersma ^b, Carine Kirkove ^c, Sandra Hol ^d, Marianne C. Aznar ^e, Albert Biete Sola ^f, Youlia M. Kirova ^g, Jean-Philippe Pignol ^h, Vincent Remouchamps ⁱ, Karolien Verhoeven ^j, Caroline Weltens ^j, Meritxell Arenas ^k, Dorota Gabrys ^l, Neil Kopek ^m, Mechthild Krause ⁿ, Dan Lundstedt ^o, Tanja Marinko ^p, Angel Montero ^q, John Yarnold ^r, Philip Poortmans ^s

Contouring

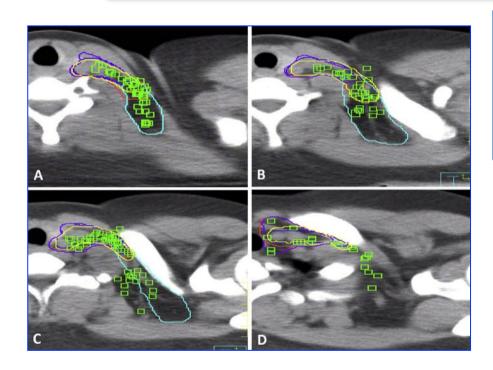


Most common site of CW recurrence (72%-100%) is within skin and subcutaneous tissues anterior to the pectoralis musculature No significant isolated recurrences in the intercostal muscles or

ESTRO guidelines: *Unless invasion was demonstrated* (T4a and T4c), there is <u>no reason</u> for <u>routinely including the major pectoral muscle and the ribs</u> in the CTV CW

A revision in the RTOG and AIRO guidelines may be warranted.

Contouring



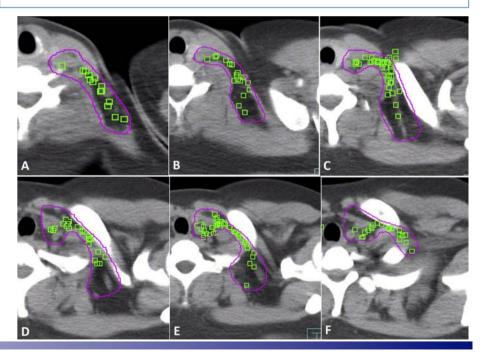
None of the atlases could fulfill >85% of coverage

CTV modification according to the results

Lateral: trapezius, clavicle, subclavicular m.

Dorsal: trapezius and subclavicular m.

Caudal: cranial edge of the sternum



Post mastectomy radiotherapy (PMRT)

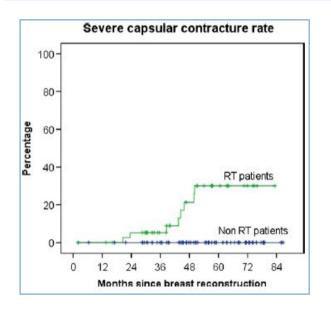
Dose

PMRT: Dose

The majority of studies: 50-50,4 Gy (1,8-2 Gy/fr)

Hypofractionation

Reconstructed breast/chest wall +/- SCN: 40 Gy in 15 fractions (2,66 Gy/fr) over 3 weeks



Median follow-up of 50 months 8/42 (19%) *severe capsule contracture*

High rate of severe capsule contracture but comparable to those with 5 week schedules

PMRT: Dose

Hypofractionation

Limited data exist with regard to hypofractionation in PMRT and regional nodal RT setting

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

Data are promising ...

....however, more data are needed to examining clinical efficacy as well as toxicity profiles

Conclusions

Volumes

Chest wall

- High Risk for LRR: pT3N+, pT4, ≥4 pN+
- Intermediate Risk for LRR: 1-3 pN+ (depending on risk factors)
- Low Risk for LRR: pT2-3 N0 (depending on *risk factors*)

Axillary nodes

No ALN-RT after complete dissection of level I and II

Internal mammary nodes

pN+ and centrally or medially located primary tumor (depending on risk factors)

Conclusions

Volumes

Supra/infraclavicular nodes

- High Risk for LRR: pT3N+, pT4, ≥4 pN+
- Intermediate Risk for LRR: 1-3 pN+ (.. risk factors..)

Contouring

RTOG Chest Wall Contouring Guidelines for Post-Mastectomy Radiation Therapy: Is It Evidence-Based?

John A. Vargo, MD, and Sushil Beriwal, MD

Atlases



Clinical Investigation

Mapping Patterns of Ipsilateral Supraclavicular Nodal Metastases in Breast Cancer: Rethinking the Clinical Target Volume for High-risk Patients

Hao Jing, MD,* Shu-Lian Wang, MD,* Jing Li, MD,† Mei Xue, MM,†

Conclusions

Dose

Standard

Total dose: 50-50,4 Gy - **Dose/fraction**: 1,8-2 Gy

Hypofractionation

