REGIONE LAZIO

SAPIENZA UNIVERSITÀ DI ROMA

AZIENDA OSPEDALIERA SANT' ANDREA

FACOLTÀ DI MEDICINA E PSICOLOGIA

Radioterapia Ipofrazionata dopo chirurgia conservativa nel trattamento delle pazienti con neoplasia mammaria: analisi preliminare di tossicità ed efficacia.

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Dott. M. Valeriani

SAPIENZA UNIVERSITÀ DI ROMA

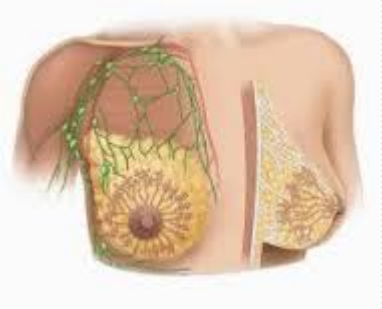
IPOFRAZIONAMENTO

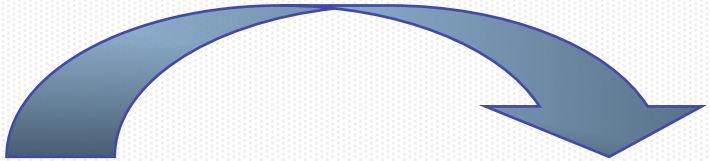
Trattamento radioterapico che prevede l'utilizzo di dosi per frazione maggiori di 2 Gy con una riduzione del numero di applicazioni

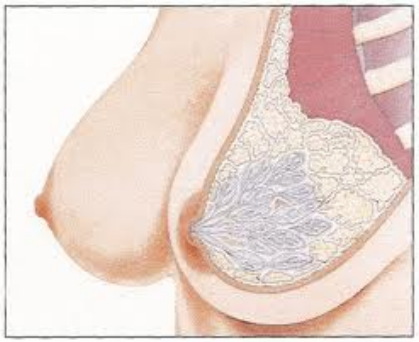
Il confronto tra l'ipofrazionamento con il frazionamento standard dimostra una sostanziale equivalenza in termini di controllo locale

I dati in letteratura

Dalla metà degli anni '90 sono stati condotti i primi studi con schemi di radioterapia non convenzionale (ipofrazionamenti) sulla mammella







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

CLINICAL INVESTIGATION **Breast**

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

Benjamin D. Smith, M.D.,* Soren M. Bentzen, Ph.D., D.Sc.,† Candace R. Correa, M.D.,‡ Carol A. Hahn, M.D.,§ Patricia H. Hardenbergh, M.D.,¶ Geoffrey S. Ibbott, Ph.D.,‖ Beryl McCormick, M.D., FACR.,# Julie R. McQueen, CHES., RHEd.,** Lori J. Pierce, M.D.,†† Simon N. Powell, M.D., Ph.D.,# Abram Recht, M.D.,§§ Alphonse G. Taghian, M.D., Ph.D.,¶¶ Frank A. Vicini, M.D., FACR.,‖‖ Julia R. White, M.D.,## and Bruce G. Haffty, M.D.***

Author/Publication	Schedule	Dosage	Selection	N°pz (BCT)
Whelan *JNCI 2002*	Standard HYPO	25x2 Gy 16x2,66 Gy	T1-2, N0 only;	612 622
Owen RMH/GOC *Lancet Oncol 2006*	Standard HYPO HYPO	25x2 Gy 13x3,3 Gy 13x3 Gy	T1-3; N-/(+ max 1 LK),	470 466 474
Bentzen/Yarnold START A *Lancet Oncol 2008*	Standard HYPO HYPO	25x2 Gy 13x3,2 Gy 13x3 Gy	T1-3; N-/+, R0 (>1mm);	749 (631) 750 (641) 737 (628)
Bentzen/Yarnold START B *Lancet Oncol 2008*	Standard HYPO	25x2 Gy 15x2,66 Gy	T1-3; N-/+, R0 (>1mm);	1105 (1020) 1110 (1018)

*

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

TOSSICITA'

Cosmesis and normal tissue effects of hypofractionated compared to standard breast radiation therapy.

Trial	Reference no.	Endpoint assessment (years)	Total dose (Gy)/fraction	Excellent/good cosmesis or no change (%)		Marked change (% or HR*)		Moderate/marked induration (% or HR*)		Skin toxicity (% or HR*)	
				5 yr	10 yr	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
START B		5	50/25	58.8		1.0		1.0		1.0	
			40/15	64.5		0.83*		0.88*		0.76*	
Canadian	28,35	5, 10	50/25	79.2	71.3			6.1	10.4	3.3	7.7
			42.5/16	77.9	69.8			4.7	11.9	3.2	8.9

Hazard ratio (HR) = *.

L'ANALISI COMPARATIVA DEGLI EFFETTI ACUTI E TARDIVI OSSERVATI NEGLI STUDI IN ESAME NON HA DIMOSTRATO UNA SOSTANZIALE DIFFERENZA TRA HF-WBI E CF-WBI

Table 1 Patient Characteristics of Randomized Trials Evaluating Hypofractionation for Whole-Breast Irradiation

	OCOG	START A	START B
	42.5Gy/16 Fractions (22 d) vs 50Gy/25 Fractions (35 d)	39 Gy/13 Fractions (5 wk) vs 41.6Gy/13 Fractions (5 wk) vs 50Gy/25 Fractions (5 wk)	40Gy/15 Fractions (3 wk) vs. 50Gy/25 Fractions (5 wk)
Number of patients randomized	1,234 patients	2,236 patients	2,215 patients
Follow-up	12 years	5 years	6 years
Inclusion criteria	Invasive carcinoma BCS pT1-T2 pN0 Uninvolved inked margin (invasive or in situ) ≤25-m width of breast tissue	Operable invasive breast cancer BCS or mastectomy pT1-3 pN0-1 M0 Clear tumour margins ≥1 mm	Operable invasive breast cancer BCS or mastectomy pT1-3 pN0-1 M0 Clear tumour margins ≥1 mm
Type of surgery (%)			
BCS	100	85	92
Mastectomy	0	15	8
Axillary dissection	100	97.3	95.6
Pathologic characteristics (%)			
Tumor size (≥2cm)	31.3	48.6	35.9
Grade 3	18.8	28.1	23
Node positive	0	28.8	22.8
Estrogen receptor negative	26		
Adjuvant treatment (%)			
Chemotherapy	10.9 (CMF in majority)	35.5 (70% anthracycline-based)	22.2 (59% anthracycline-based)
Tamoxifen	41.8	78.6	87.1
Radiation treatment (%)			
Regional radiation	0	14	7.3
Boost on surgical bed	0	61	42.6

Abbreviations: BCS, breast-conserving surgery; CMF, cyclophosphamide, methotrexate, and fluorouracil.

Table 2 Results of Randomized Trials Evaluating Hypofractionation for WBI*

	OCOG		START A			START B	
	50Gy/25fx	42.5Gy/16fx	50Gy/25fx	41.6Gy/13fx	39Gy/13fx	50Gy/25fx	40Gy/15fx
Number of patients	612	622	749	750	737	1,105	1,110
Local recurrence, 5 y (%)**	3.2	2.8	3.6	3.5	5.2	3.3	2.2
Absolute difference (%) (95% CI)	0.4 (1.5–2.4)			0.2 (−1.3 to 2.6)	0.9 (−0.8 to 3.7)	−0.7 (−1.7 to 0.9)	
Local recurrence, 10 y (%)**	6.7	6.2†					
Absolute difference (95% CI)	0.5 (−2.5 to 3.5)						
Survival, 5 y (%)	91.7	92.3	88.8	88.1	88.7	87.5	90.4‡
Survival, 10 y (%)	84.4	84.6					
Toxicities, 5 y (%)							
Skin§	17.7% (3.3)	13.9 (3.2)	31.1	25.0	21.6‡	27.8	22.9‡
Subcutaneous tissue‖	38.6% (6.1)	34.2 (4.7)	42.6	44.6	34.9	42.3	38.2
Toxicities, 10 y (%)							
Skin¶	29.5% (7.7)	33.2 (8.9)					
Subcutaneous tissue¶	54.7% (10.4)	51.9 (11.9)					
Adverse cosmetic (%)	Fair and Poor	Fair and Poor		Change in breast appearance (picture)		Change in breast appearance (picture)	
5 years	20.8	22.1	42.9	43.6	32.1‡	42.2	36.5
10 years	28.7	30.2					

Abbreviations: LR, local recurrence; LRR, locoregional recurrence; OS, overall survival, CI, confidence interval.

*Comparison within trial are non significant unless otherwise specified.

†$P < .001$ for noninferiority.

‡$P < .05$ as compared with 50 Gy.

§Grades 1 to 3 (grades 2-3) RTOG/EORTC late radiation morbidity score for Canadian trial. Moderate or marked change in skin appearance by patient for START trials.

‖Grades 1 to 3 (grades 2-3) RTOG/EORTC late radiation morbidity score for Canadian trial. Moderate or marked change in breast hardness by patient for START trials.

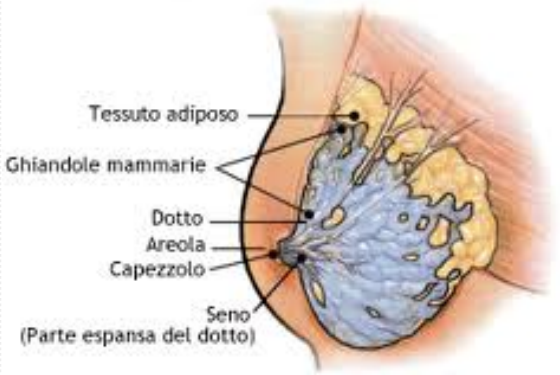
¶Grades 1 to 3 (grade 2-3) RTOG/EORTC late radiation morbidity score.

**Local recurrence for Canadian trial; local regional recurrence for START trials.

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

Background 5-year results of the UK Standardisation of Breast Radiotherapy (START) trials suggested that lower total doses of radiotherapy delivered in fewer, larger doses (fractions) are at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions) for women after primary surgery for early breast cancer. In this prespecified analysis, we report the 10-year follow-up of the START trials testing 13 fraction and 15 fraction regimens.



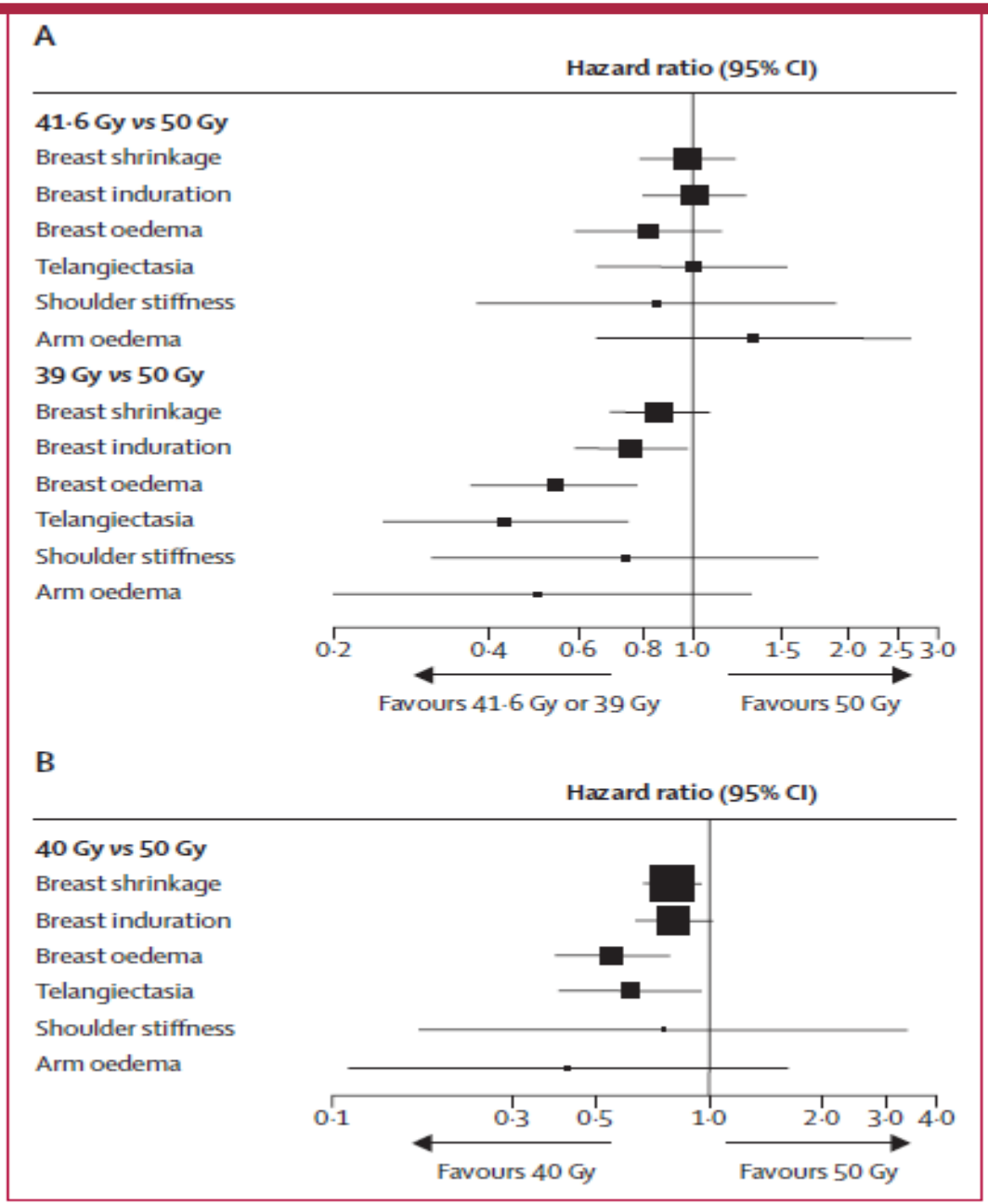


Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.

	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**

	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*
Local relapse					
50 Gy	50/1105 (4·5%)	3·3% (2·4–4·6)	5·2% (3·9–6·9)	1·00	..
40 Gy	36/1110 (3·2%)	1·9% (1·2–3·0)	3·8% (2·7–5·2)	0·70 (0·46–1·07)	0·10
Local-regional relapse					
50 Gy	53/1105 (4·8%)	3·5% (2·5–4·8)	5·5% (4·2–7·2)	1·00	..
40 Gy	42/1110 (3·8%)	2·3% (1·5–3·4)	4·3% (3·2–5·9)	0·77 (0·51–1·16)	0·21
Distant relapse					
50 Gy	158/1105 (14·3%)	10·5% (8·8–12·5)	16·0% (13·8–18·5)	1·00	..
40 Gy	121/1110 (10·9%)	7·5% (6·0–9·2)	12·3% (10·3–14·6)	0·74 (0·59–0·94)	0·014
Any breast cancer-related event†					
50 Gy	222/1105 (20·1%)	14·3% (12·3–16·5)	22·2% (19·7–25·0)	1·00	..
40 Gy	182/1110 (16·4%)	10·4% (8·7–12·4)	18·3% (16·0–20·9)	0·79 (0·65–0·97)	0·022
All-cause mortality					
50 Gy	192/1105 (17·4%)	10·9% (9·1–12·9)	19·2% (16·8–21·9)	1·00	..
40 Gy	159/1110 (14·3%)	7·9% (6·4–9·6)	15·9% (13·7–18·4)	0·80 (0·65–0·99)	0·042

*Assessed with log-rank test compared with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 4: **Relapse and mortality according to fractionation schedule in START-B**

Premesse

- La radioterapia ipofrazionata presenta gli stessi risultati in termini di controllo locale e di tossicità rispetto al frazionamento standard con riduzione del tempo totale di trattamento

- Una grande varietà di regimi ipofrazionati sono stati adottati nel trattamento adiuvante alla chirurgia conservativa.

Scopo

- Valutare la tossicità e l'efficacia di uno schema di trattamento ipofrazionato della durata complessiva di 4 settimane.

Materiali e metodi 1

- Periodo: Giugno 2008-Marzo 2013

- N= 223
- Età mediana= 60 anni

CHT Adiuvante/ Neoadiuvante
70 (31.4%)

- Trattamento: radioterapia adiuvante ipofrazionata

- Schema: 42.4 Gy in 16 frazioni sull'intera mammella seguiti da 4 frazioni di 2.5 Gy sul letto chirurgico. Tutte le pazienti erano state sottoposte a chirurgia conservativa.

N = 223 (%)	
< 50 anni	≥ 50 anni
37 (16.6)	186 (84.7)

Materiali e metodi 2

N=223 (%)	T	N=223(%)	N
4 (1.7)	pT0	181 (81.2)	pN0
26 (11.7)	pTis	42 (18.8)	pN1
156 (70)	pT1		
37 (16.6)	pT2		

Grading istologico

N=223 (%)	G
37 (16.6)	G1
106 (47.5)	G2
80 (35.9)	G3

Tabella RTOG/EORTC di valutazione della tossicità acuta e tardiva

GRADO	Tossicità Acuta	Tossicità tardiva
0	Nessun Cambiamento	Nessun cambiamento
1	Eritema follicolare,lieve ipercromia,desquamazione secca,ridotta sudorazione	Leggera atrofia e secchezza
2	Eritema brillante,desquamazione umida a chiazze,edema moderato,totale perdita di peli	Moderata atrofia e telangectasia
3	Desquamazione umida confluente,edema importante,telangectasie	Atrofia rilevante con completa secchezza
4	Ulcerazione,Emorragia,necrosi	Ulcerazione

Risultati 1

Follow-up mediano= 16 mesi (range 3-54 mesi)

N=223 (%)	¶ Î Tossicità acuta	N=223(%)	Tossicità tardiva
9 (4)	G0	170 (76.2)	G0
197 (88.3)	G1	45 (20.2)	G1
16 (7.2)	G2	8 (13.6)	G2
1 (0.5)	G3		

¶ Tossicità acuta cutanea

Î Tossicità valutata secondo scala RTOG

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	OCOG		START A			START B	
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Local recurrence, 10 y (%)**	6.7	6.2†					
Absolute difference (95% CI)	0.5 (−2.5 to 3.5)						
Survival, 5 y (%)	91.7	92.3	88.8	88.1	88.7	87.5	90.4‡
Survival, 10 y (%)	84.4	84.6					
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Subcutaneous tissue‖	38.6% (6.1)	34.2 (4.7)	42.6	44.6	34.9	42.3	38.2
Toxicities, 10 y (%)							
Skin¶	29.5% (7.7)	33.2 (8.9)					
Subcutaneous tissue¶	54.7% (10.4)	51.9 (11.9)					
Adverse cosmetic (%)	Fair and Poor	Fair and Poor		Change in breast appearance (picture)		Change in breast appearance (picture)	
5 years	20.8	22.1	42.9	43.6	32.1‡	42.2	36.5
10 years	28.7	30.2					

Abbreviations: LR, local recurrence; LRR, locoregional recurrence; OS, overall survival, CI, confidence interval.

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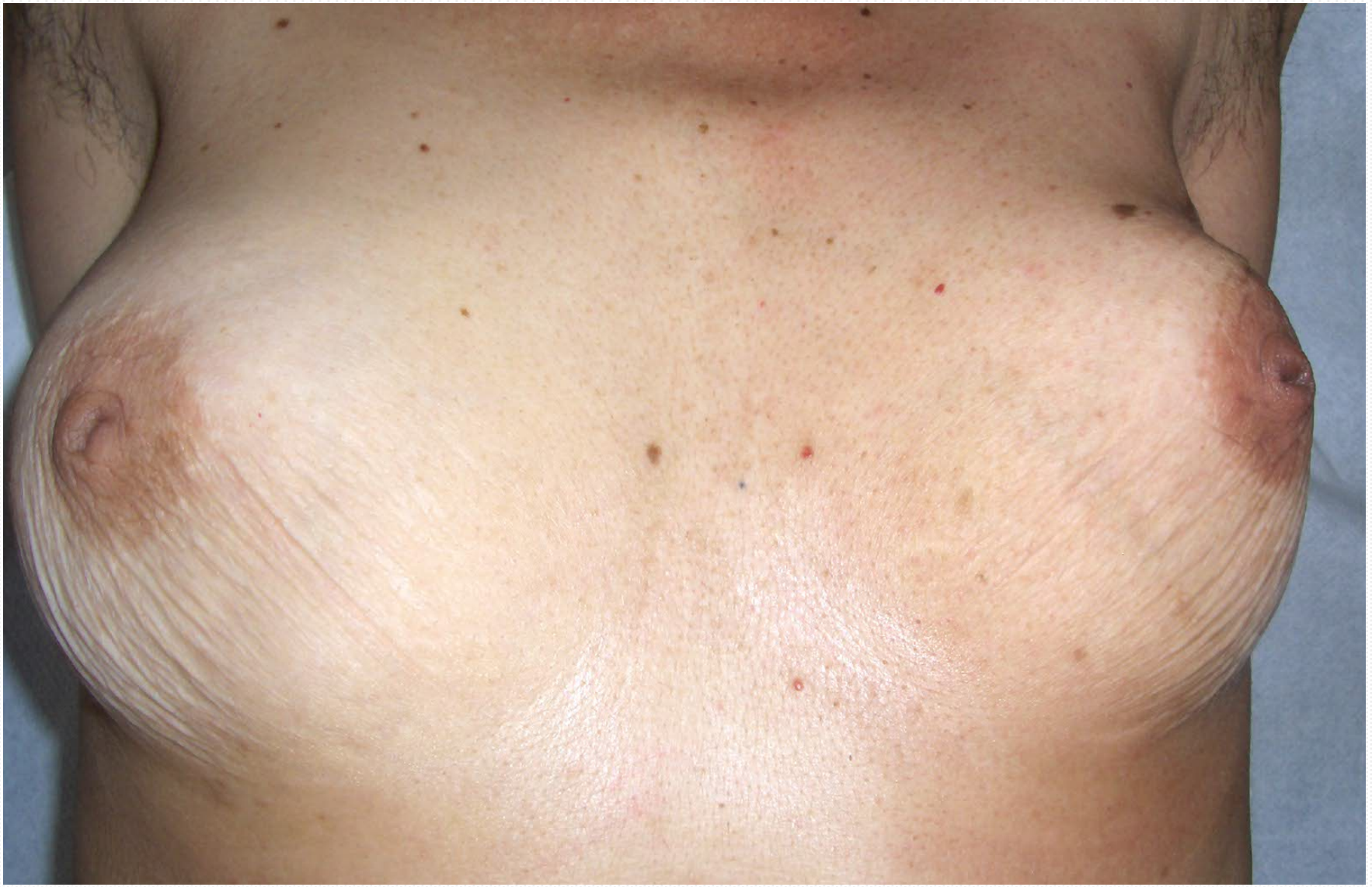
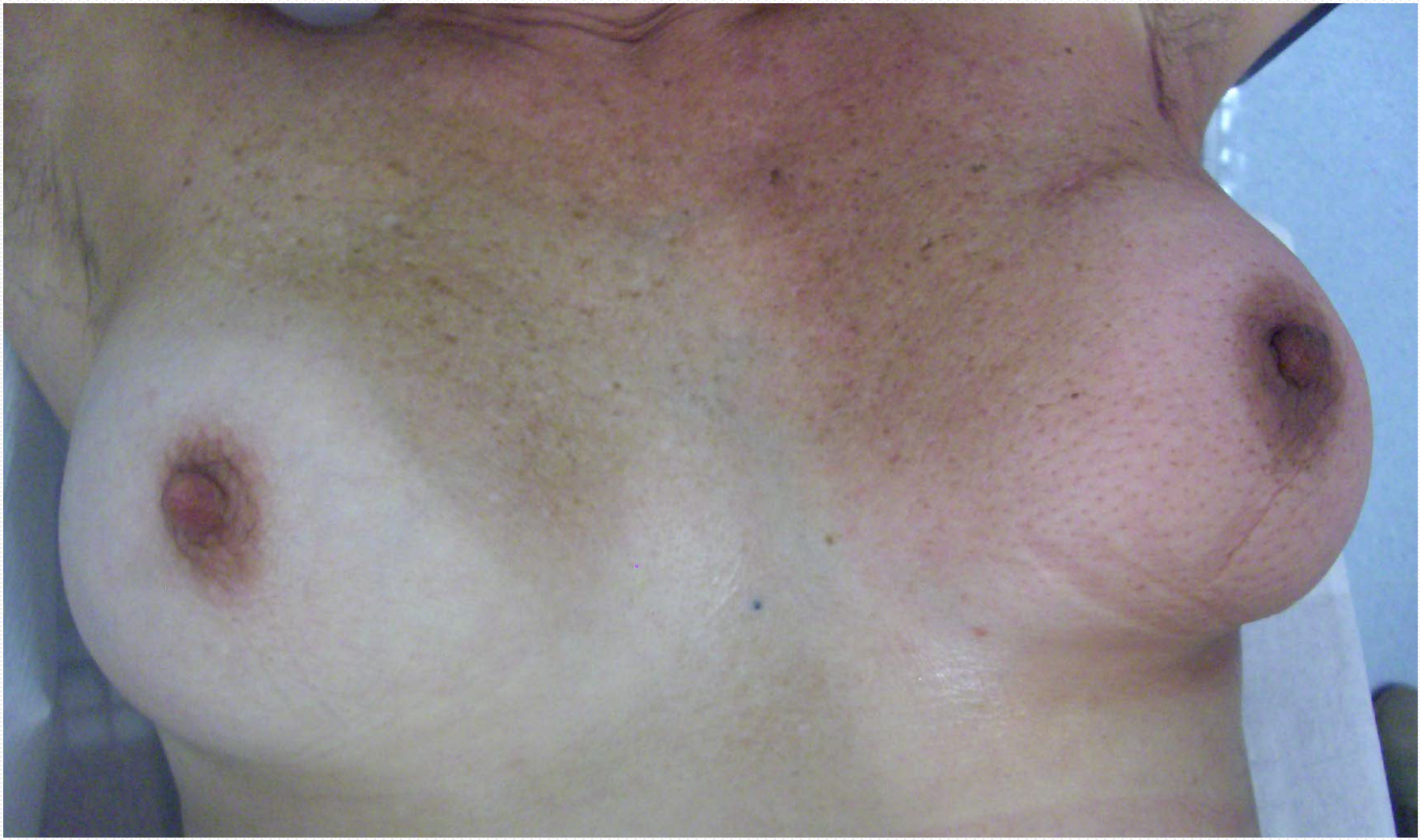


TERMINE RT
MAMMELLA SN



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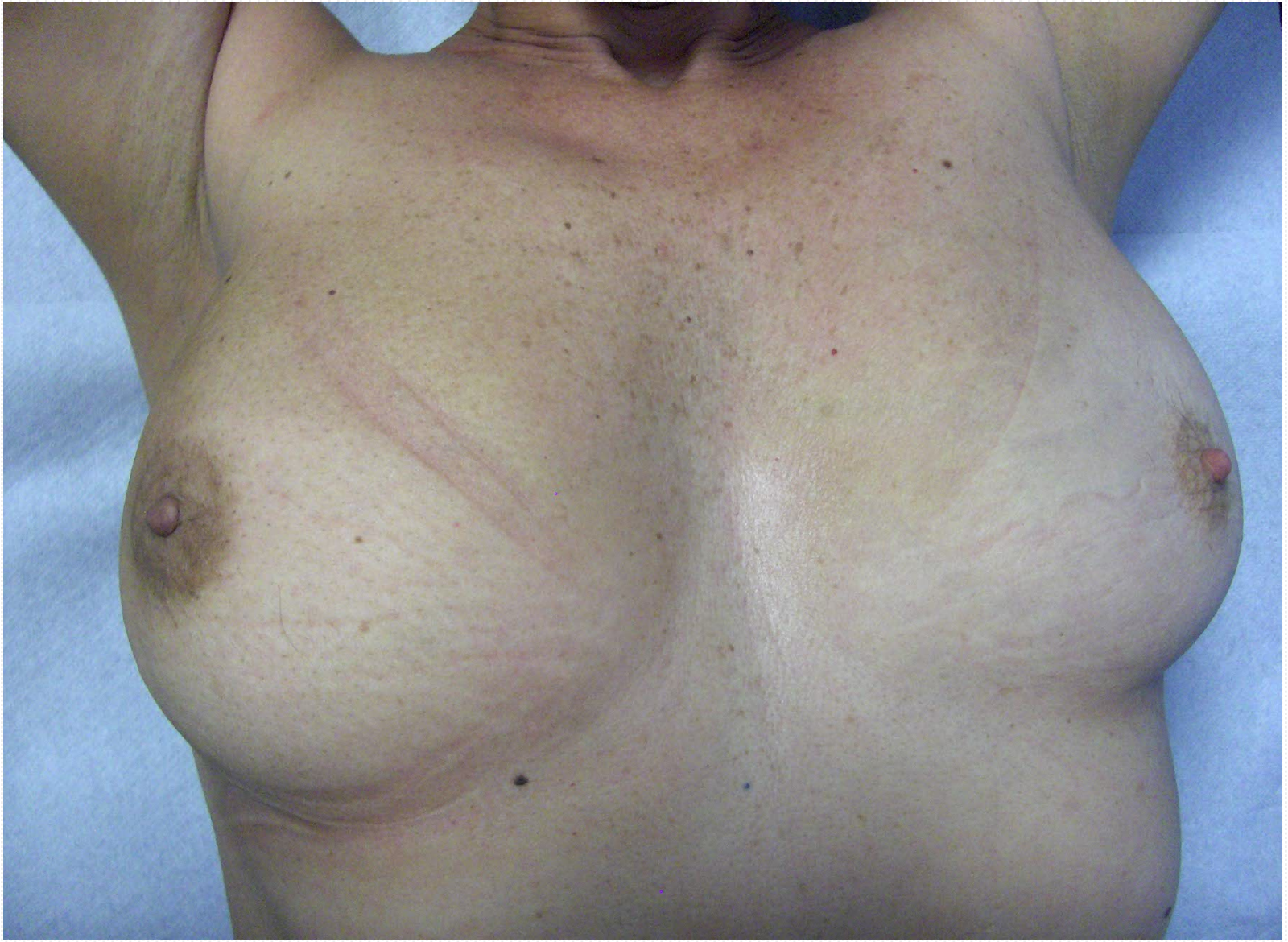
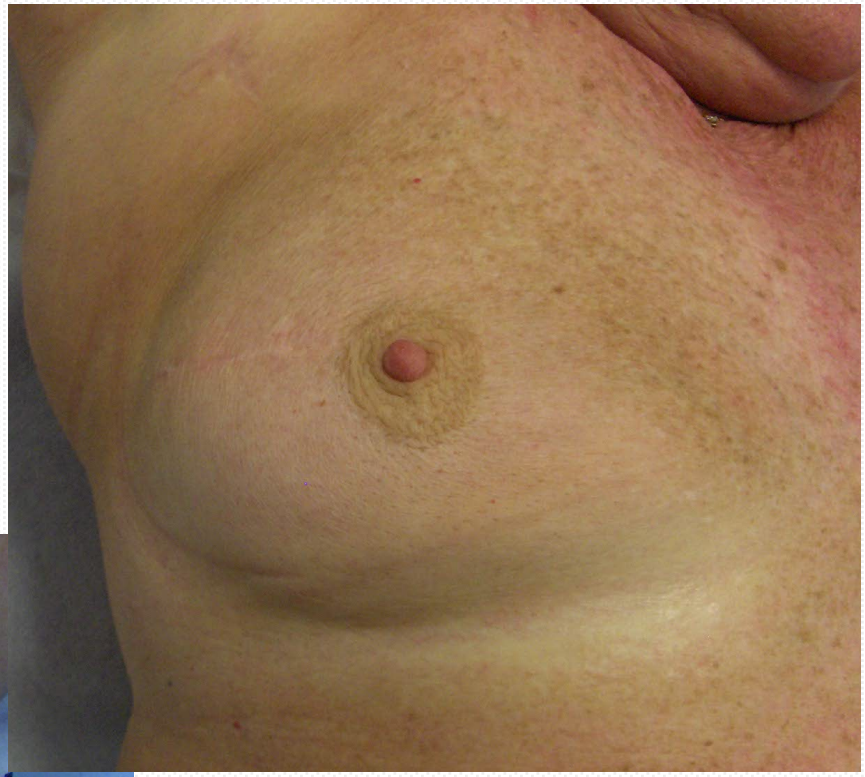
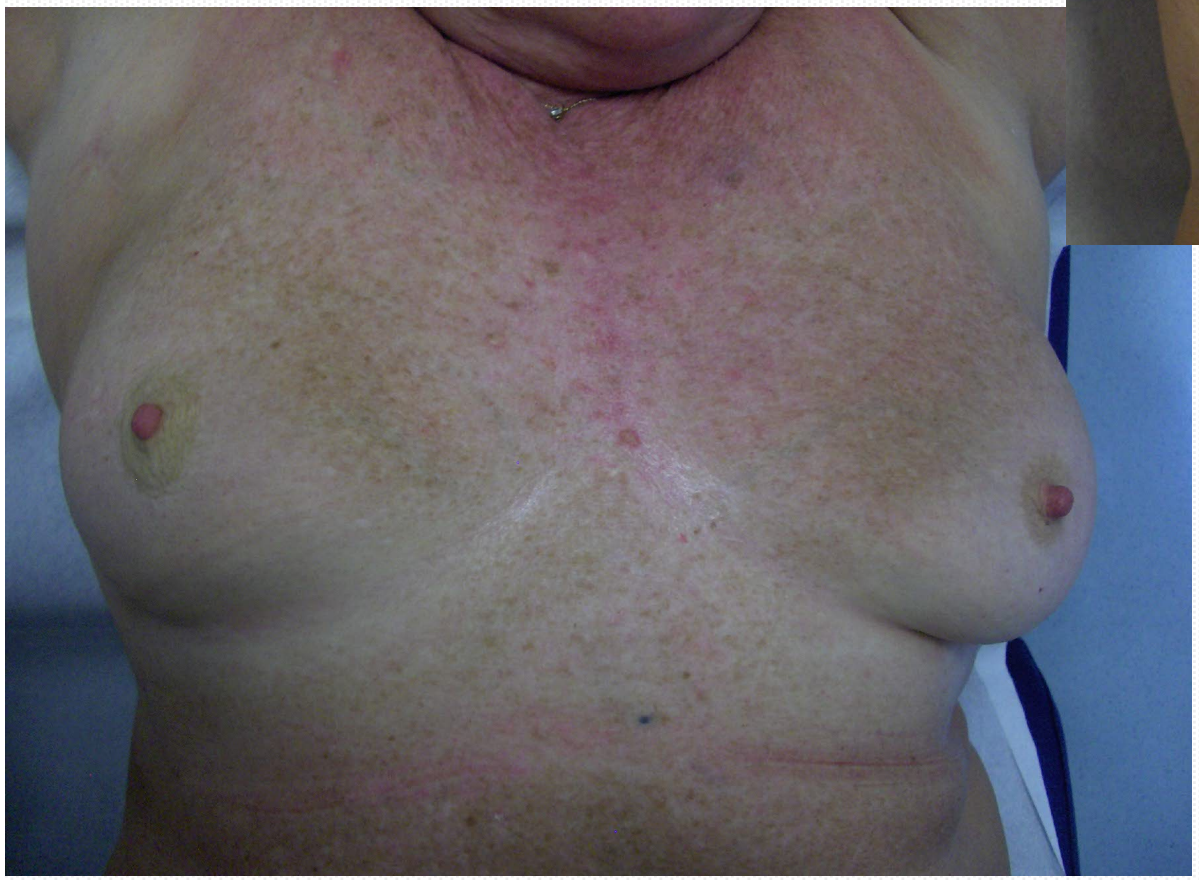
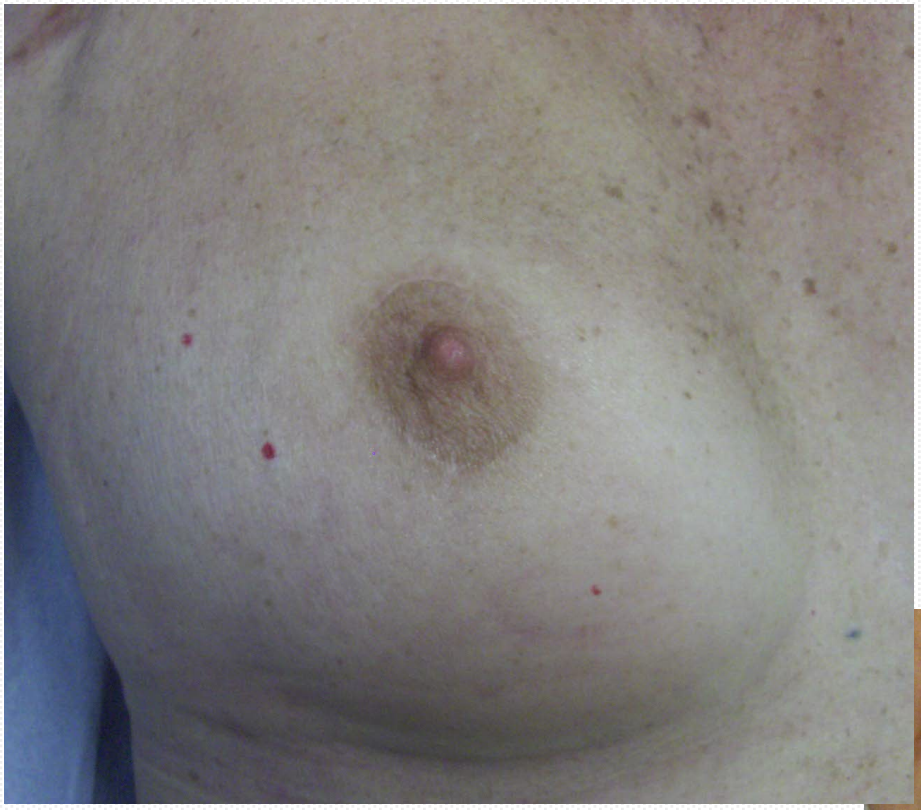


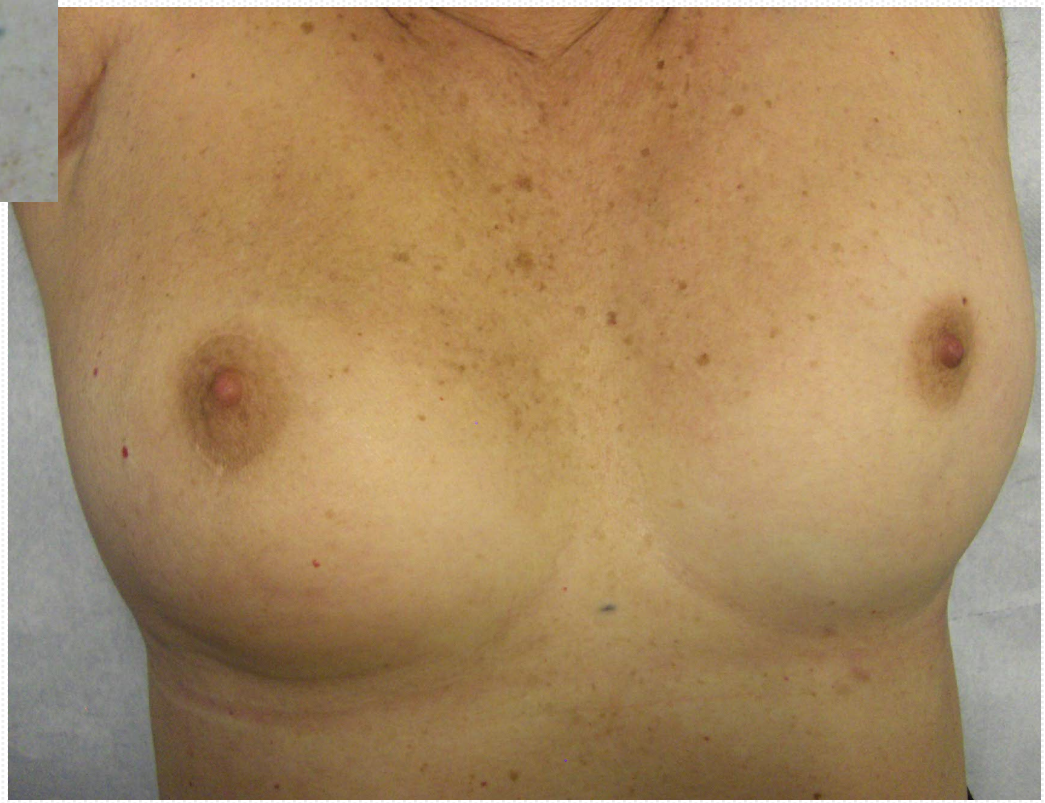
DOPO 6 MESI DAL TERMINE RT
MAMMELLA DX



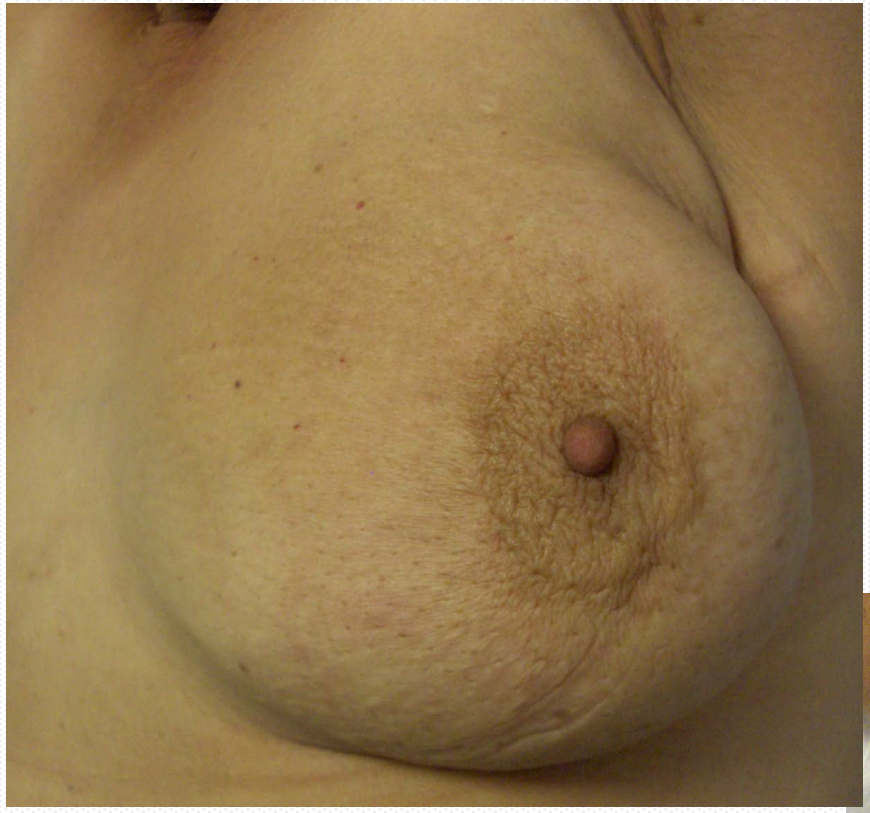


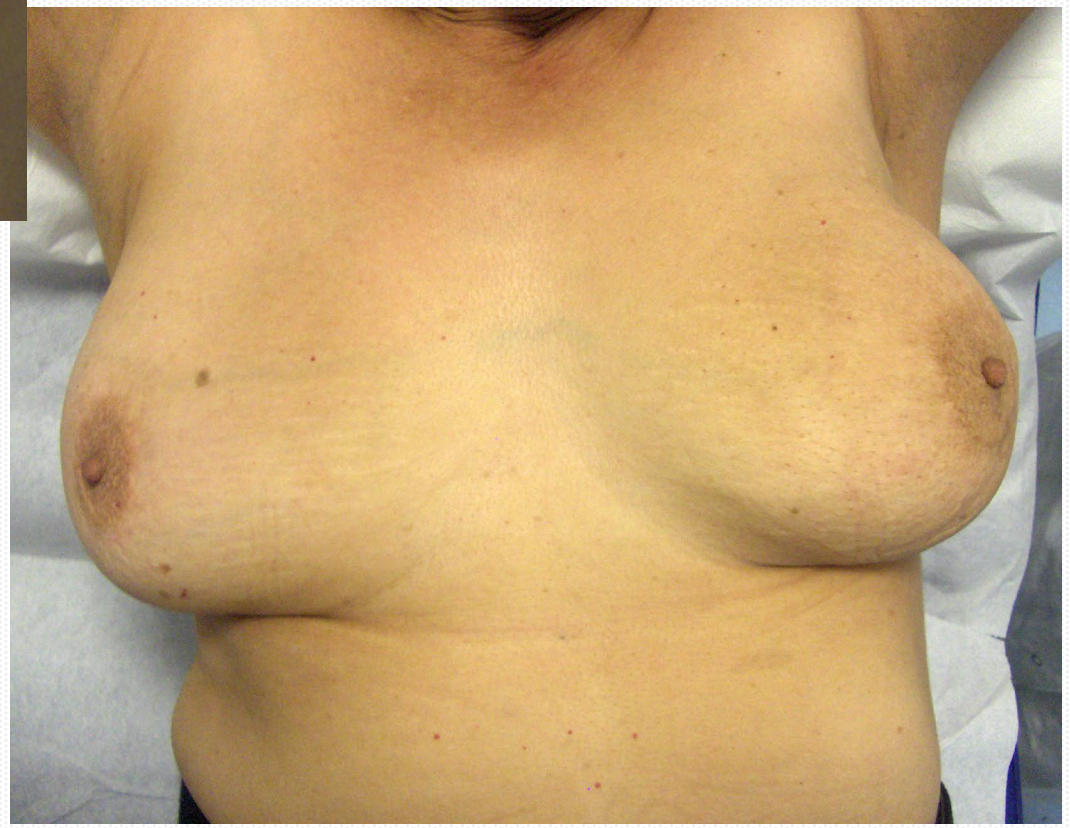
DOPO 7 MESI DAL TERMINE RT MAMMELLA DX





DOPO 13 MESI DAL TERMINE RT MAMMELLA DX





DOPO 24 MESI
DAL TERMINE
RT
MAMMELLA SN

Risultati 2

N=223		
Recidiva locale	Metastasi	¶ Decesso
2 (0.9)	3 (1.34)	4 (1.8)

¶ Cause non correlate alla malattia

Conclusioni

- Il trattamento ipofrazionato utilizzato nel nostro studio si è dimostrato ben tollerato in termini di tossicità acuta e di tossicità tardiva.

- I dati preliminari sul controllo locale di malattia sono incoraggianti.

- Necessario un follow-up più lungo per valutazioni definitive.