

Protesi, espansori e chirurgia oncoplastica: quale approccio nell'impostazione del trattamento radioterapico?



Discussant
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RT e ricostruzione mammaria

- Studi retrospettivi o retrospettivo controllato
- Eterogeneità dati: modalità ricostruttive, delayed-immediate reconstruction, timing RT
- numero limitato di pazienti
- mancanza di studi R → metanalisi, review sistematiche
- Dati più recenti migliori → miglioramento tecnica chirurgica e trattamento RT

DIBATTITO

- ✓ Quale tipo di ricostruzione migliore se RT?
- ✓ Timing ricostruzione/RT prima o dopo?
- ✓ Modalità RT

Chen SA et al. Radiat Oncol 2013

Sensus-Konefka E et al. Cancer Treat Rev 30:671-682, 2004

Barry M, Kell MR. Breast Cancer Res Treat 127:15-22, 2011

Rozen WR, Ashton MW. Gland Surgery 2012

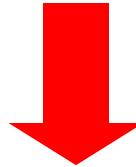
Berbers J et al. Eur J Cancer 2014

Walsh SM et al. The Surgeon 2014

Rochlin DH et al. J Surg Oncol 2015

Meccanismi del danno radioindotto

- Danno cellule endoteliali
- Alterazione della microcircolazione
diabete, fumo, età....
- Fibrosi
- Atrofia cutanea



- Alterazione letto protesico
- Danno vascolare lembo

Fattori relativi alla paziente interferenti con risultato cosmetico e complicanze

- Età
- Obesità/BMI
- Ipertensione arteriosa/Vasculopatie
- Diabete
- Fumo

NB selezione pazienti candidabili ≠ modalità

Chawla et al, Int J Radiat Oncol Biol Phys, 2002

Williams et al, Ann Surg, 1995

Lipa et al, Plast Reconstr Surg, 2003

McCarthy CM et al Plast Reconstr Surg 121:1886-1892, 2008

Aristei C et al. Strahlenther Onkol 188:1079-1074, 2012

Chiru MR, Lascăr I J Med Life, 6:462-463, 2013

Khansa I et al. Plast Reconstr Surg, 131:443-452, 2013

Carnevale A et al Radiol Med 118:1240-1250, 2013

Eriksson M et al Breast Cancer Res Treat 142:591-601, 2013

Hanwright PJ et al Breast 22:938-945, 2013

Fischer JP et al J Am Coll Surg 217:780-787, 2013

Fattori relativi al trattamento interferenti con risultato cosmetico e complicanze

- ✓ RT e modalità trattamento radiante
- ✓ Timing ricostruzione-RT
- ✓ Tipo di ricostruzione
- ✓ Esperienza operatore
- ✓ Infezione perioperatoria
- ✓ Terapia sistemica
 - chemiotp
ormonotp
 - radiosensibilizzazione
 - TGF β modulatore fibrosi

Chawla Ak et al Int J Radiat Oncol Biol Phys 54:520-526, 2002
Tallet et al, Int J Radiat Oncol Biol Phys, 2003
Cowen D Breast Cancer Res Treat 121:627-634, 2010
Khansa I et al. Plast Reconstruct Surg, 131:443-452, 2013
Eriksson M et al Breast Cancer Res Treat 142:591-601, 2013
Li L et al. J Plast Reconstruct Aesthet Surg, 67:461-7, 2014
Lam TC et al. Plast Reconstr Surg 2013

Tipo di ricostruzione

- **Ricostruzione con tessuto autologo**

Incidenza complicanze 7-88%

Soddisfazione pazienti e cosmesi buono 17-100%

Tran et al, Plast Reconstruct Surg, 2001

Zimmerman et al, Am J Clin Oncol, 1998

Hunt et al, Ann Surg Oncol, 1997

Sensus-Konefka E et al Cancer Treat Rev 30:671-682, 2004

Jhaveri Jd et al. Int J Radiat Oncol Biol Phys 2008

Hughes K et al. Anticancer Res 2012

Pestana IA et al. Ann Plast Surg 2013

- **Ricostruzione con espansore/protesi**

Incidenza complicanze 17-80%

soddisfazione pazienti e cosmesi buono 7-88%

Krueger et al, Int J Radiat Oncol Biol Phys, 2001

Tallet et al, Int J Radiat Oncol Biol Phys, 2003

Spear et al, Plast Reconstruct Surg, 2000

Sensus-Konefka E et al Cancer Treat Rev 30:671-682, 2004

Aristei C et al. Strahlenther Onkol 188:1079-1074, 2012

Kronowitz SJ Plast Reconstr Surg 130:513-523, 2012

Lam TC et al. Plast Reconstr Surg 2013

Pestana IA et al. Ann Plast Surg 2013

Table 1 Cosmesis and risk of complications in patients undergoing prosthetic reconstruction and radiotherapy.

References	Method of reconstruction	Timing of radiotherapy	Irradiated patients		Non-irradiated patients	
			Acceptable cosmesis	Complications	Acceptable cosmesis	Complications
Chu ²⁸	Prosthetic	After R	28/32 (88%)	NR	—	—
Ryu ⁶⁷	Prosthetic	After R	5/7 (71%)	2/7 (29%)	—	—
Halpern ⁶⁶	Prosthetic	After R	1/7 (14%)	NR	—	—
von Smitten ⁶⁵	Prosthetic	After R	1/15 (7%)	12/15 (80%)	13/15 (87%)	3/15 (20%)
Kraemer ⁶⁴	Prosthetic	Before R	11/35 (31%)	23/35 (66%)	71/111 (64%)	31/111 (28%)
Forman ⁶³	Prosthetic	Before R	4/10 (40%)	3/10 (30%)	—	—
Vandeweyer ⁶²	Prosthetic	After R	0/6	1/6 (17%)	114/118 (96.6%)	11/118 (9%)
Rosato ⁵⁷	Prosthetic	After R	4/15 (27%)	NR	171/190 (90%)	NR
Victor ⁵⁴	Prosthetic	After R	7/13 (54%)	NR	—	—
Krueger ²²	Prosthetic	Various	NR	13/19 (68%)	NR	19/62 (31%)
Contant ⁵⁰	Prosthetic	Various	NR	14/28 (50%)	NR	10/87 (11%)
Chawla ²¹	Prosthetic	Various	7/18 (39%)	10/18 (55%)	—	—
Paulhe ⁶¹	Prosthetic	Before R	13/26 (50%)	NR	17/24 (71%)	NR
Stabile ⁷	Prosthetic	Before R	7/9 (78%)	0	—	—
Fodor ⁶⁹	Prosthetic	Before R	NR	50%	NR	40%
Ramon ⁵²	Prosthetic	After R	NR	6/11 (54.6%)	NR	3/41 (7.3%)
Olenius ¹⁹	Prosthetic	Before R	5/11 (45%)	NR	25/31 (78%)	NR
Noone ⁹	Prosthetic	After R	NR	7/12 (58%)	—	—
Barreau-Pouhaert ⁷⁰	Prosthetic	Before R	NR	3/22 (27.3%)	NR	12/109 (11%)
		After R	NR	6/11 (54.6%)	NR	3/100 (3%)
Tallet ⁵⁶	Prosthetic	Various	45%	28/55 (51%)	80%	3/22 (14%)
Schuster ⁵¹	Prosthetic+autologous flap	Various	17/51 (33.3%)	NR	—	—
Evans ⁶⁸	Prosthetic+autologous flap	Various	NR	16/39 (41%)	NR	39/338 (12%)
Spear ⁴	Prosthetic+autologous flap	Various	NR	21/40 (53%)	NR	4/40 (10%)
Total			110/255 (43%)	165/328 (50%)	411/489 (84%)	138/1043 (13%)

NR = not reported, R = reconstruction.

Table 2 Cosmesis and risk of complications in patients undergoing autologous reconstruction and radiotherapy.

References	Method of reconstruction	Timing of radiotherapy	Irradiated patients		Non-irradiated patients	
			Acceptable cosmesis	Complications	Acceptable cosmesis	Complications
Zimmerman ⁸⁰	TRAM	After R	18/20 (90%)	0	—	—
Kuske ⁵	TRAM	Before R	7/8 (88%)	5/8 (63%)	—	—
Williams ⁴⁶	TRAM	Before R	NR	27/108 (25%)	NR	98/572 (17%)
Williams ⁵⁵	TRAM	After R	NR	10/19 (53%)	NR	98/572 (17%)
Tran ¹⁷	TRAM	After R	NR	> 88%	—	—
		Before R	NR	≤ 23%	—	—
Moran ³⁶	TRAM	Before R	"Excellent cosmesis"	2/16 (13%)	—	—
Chawla ²¹	TRAM	Various	26/30 (87%)	5/30 (17%)	—	—
Tran ²³	TRAM	After R	7/41 (17%)	NR	—	—
Jacobsen ⁵⁴	TRAM	Before R	NR	7/47 (15%)	NR	33/112 (29%)
Hartampf ¹⁶	TRAM	Before R	NR	6/52 (11.5%)	NR	13/248 (5%)
Watterson ⁴⁹	TRAM	Before R	NR	34/91 (37.4%)	NR	98/465 (21.1%)
Disa ⁷⁴	TRAM	Before R	8/8 (100%)	2/8 (25%)	—	—
Missana ⁸²	TRAM		100%	NR	—	—
Schuster ⁵³	TRAM	Before R	7/8 (87.5%)	NR	—	—
Hunt ⁷⁹	TRAM	After R	16/19 (84%)	2/19 (10.5%)	—	—
Proulx ¹²	TRAM	Various	14/15 (93.3%)	1/15 (6.7%)	—	—
Kroll ⁸¹	TRAM	Before R	54/82 (66%)	22/66 (33%)	NR	33/158 (21%)
	LD	Before R		10/16 (63%)		18/44 (41%)
Disa ⁷⁴	LD + prosthetic	Before R	1/3 (33%)	2/3 (67%)	—	—
Missana ⁸²	LD + prosthetic	After R	29%	NR	—	—
Nash ⁸³	LD + prosthetic	Before R	29/29 (100%)	0	—	—
Rogers ²⁴	DIEP	After R	NR	17/30 (56.7%)	NR	0
Kuske ⁵	Other autologous or prosthetic	Various	34/61 (56%)	29/63 (46%)	—	—
Total			221/324 (68%)	181/591 (31%)	NR	293/1599 (18%)

DIEP = deep inferior epigastric perforator flap, LD = latissimus dorsi myocutaneous flap, NR = not reported, R = reconstruction, TRAM = transverse rectus abdominis myocutaneous flap.

Tipo di ricostruzione e RT

Radiotherapy and breast reconstruction: a meta-analysis.

11 studi, 1105 pts, ≠ modalità ricostruzione

Ricostruzione con tessuti autologhi minori complicanze

OR 0.21, 95% CI, 0.1-0.4 autologo vs E/I

Table 3 Effect of radiotherapy on implant versus autologous breast reconstruction

Author	TOR	Patient no.	MOR	Radiotherapy	Complications (%)
Anderson et al. [11]	Immediate	35	Autolog.	Yes	0
	Immediate	50	Implant/Ex	Yes	5
Jhaveri et al. [29]	Immediate	23	Autolog.	Yes	8.7
	Immediate	69	Implant	Yes	55
Wong et al. [10]	Immediate	47	Autolog	Yes	9
	Immediate	15	Implant based	Yes	40
Stralman et al. [22]	Immediate	59	Autolog	Yes	13.5
	Immediate	82	Implant	Yes	34
Total	Immediate	164	Autolog	Yes	7.8
Total	Immediate	216	Implant	Yes	33.5

TOR timing of reconstruction, MOR method of reconstruction, Ex expander, Autolog autologous reconstruction

Tipo di ricostruzione

Ricostruzione E/I + RT

Incidenza complicanze

- Infezione 37-3.7%
- Necrosi 12.7%
- Reintervento 37-3.6%

Barry M, Kell MR. Breast Cancer Res Treat 2011
Hughes K et al. Anticancer Res 2012
Lam TC et al. Plast Reconstr Surg 2013

- > chirurgia non pianificata o correttiva con RT
- Maggioranza mantengono impianto
- Solo minoranza conversione ad autologo
- Circa 1/3 pz continua a sviluppare contrattura capsulare Baker III or IV

Kronowitz SJ. Plast Reconstr Surg 2012

Contrattura capsulare

Grado Classificazione di Baker

- I *Impianto protesico non palpabile e non visibile*
 - II *Impianto protesico lievemente indurito, palpabile ma non visibile*
 - III *Impianto protesico indurito con iniziale alterazione della forma, poco mobile, palpabile e visibile*
 - IV *Impianto protesico di consistenza dura con distorsione marcata della morfologia, dolente e dolorabile*
-

Modificato 1995

Spear SL, Baker JL Plast Reconstr
Surg 96:1119-1123, 1995

Incidenza contrattura capsulare	RT	no RT
	38.6%-41.7%	14.1%-14.5%

Contrattura III-IV ~ 20%

Benediktsson L, Perbeck L. J Plast Reconstr Aesthet Surg, 2006

Behranwala KA et al. J Plast Reconstr Aesthet Surg, 2006

Tipo di ricostruzione tessuto autologo + RT

Review 25 studi 3900 pz

	RT	no RT	
• Liponecrosi	23.8% vs 8.5%		p=0.006
• Complicanze globali	33.9% vs 28.6%		p=0.59
• Revisione chirurgica	18.3% vs 16.1%		p=0.38

Schaverien MV et al. J Plast, Reconstr Aesthet Surg, 66:1637-1651, 2013



Review 11 studi 337 pz

• Liponecrosi	16.9%
• Revisione chirurgica	24%
• Fibrosi	16.9%
• Contrattura	35.4%

Rochlin DH et al. J Surg Oncol, 2015

Timing ricostruzione/RT

RT prima o dopo ≠ modalità ricostruzione



- Tessuto autologo
- Espansore impianto

non differenze SS complicanze

≠ tipo complicanze

early: Ric pre-RT, late: Ric post-RT

Adesiyun TA et al. Int J Radiat Oncol Biol Phys 2011

Schaverien MV et al. J Plast, Reconstr Aesthet Surg, 66:1637-1651, 2013

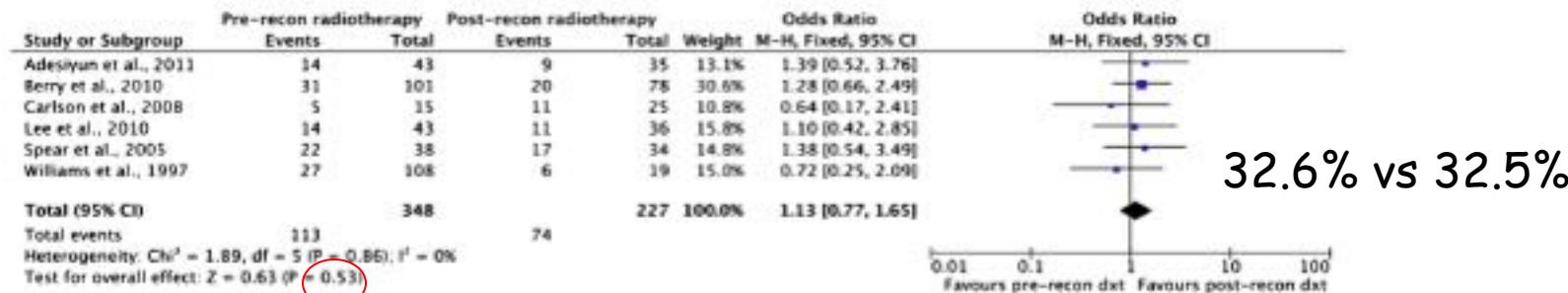
Kelley BP et al. Ann Surg Oncol 2014

Momoh AO et al. Ann Surg Oncol 21:118-124, 2014

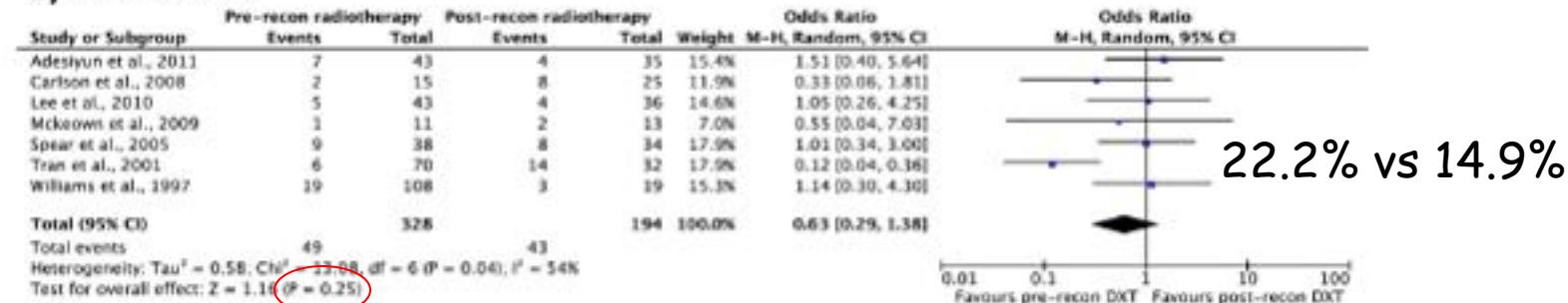
Autologo: Ricostruzione pre RT vs ricostruzione post RT

Review sistematica 25 studi Da Schaverien MV et al. J Plast, Reconstr Aesthet Surg, 2013

a) Overall complications



b) Fat necrosis



c) Revisional surgery

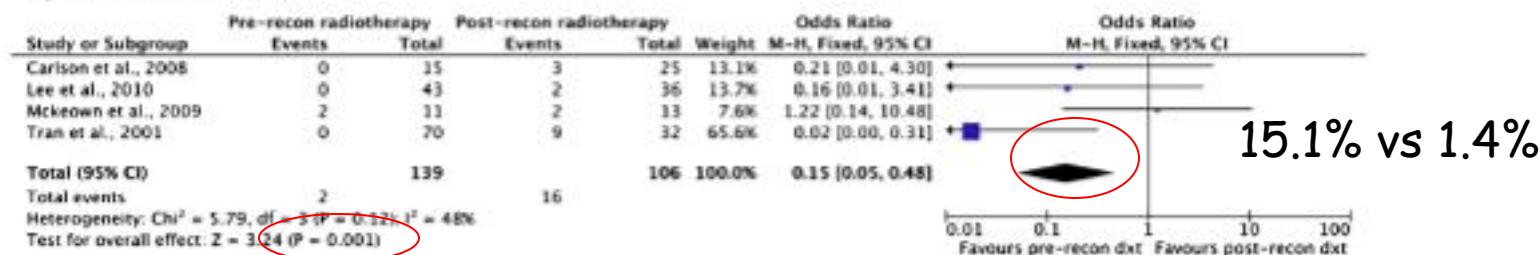


Figure 3 Meta-analysis of pooled data from observational studies comparing patients that received immediate autologous breast reconstruction and postoperative radiotherapy with patients that received radiotherapy before delayed autologous reconstruction included in Table 3; a) Forest plot of prevalence of complications; b) Forest plot of prevalence of fat necrosis; c) Forest plot of prevalence of revisional surgery.

Dati coerenti con review di Kelley 2014

Timing RT e Ricostruzione E/I

Ricostruzione post RT 42%

Fallimento ricostruzione

Ricostruzione pre RT 25%

Pestana IA et al. Ann Plast Surg 2013



26 studi, impianto protesico

- ✓ Complicanze RT-pre vs RT-post ricostr → No diff SS
- ✓ Contrattura capsulare I-II e III-IV → No diff SS
- ✓ Fallimento impianto 19% RT-pre vs 20% RT-post

Momoh AO et al. Ann Surg Oncol 21:118-124, 2014

Complicanze e cosmesi secondo tipo di ricostruzione e timing RT

Da Berbers J et al. Eur J Cancer 2014

Complication rate and cosmetic outcome categorised by the timing of radiotherapy and subdivided in autologous and implant reconstructions.*

Complications	Radiotherapy first				Reconstruction first			
	Autologous		Implant		Autologous		Implant	
	Reported incidences	Weighted mean (95%-CI) **	Reported incidences	Weighted mean (95%-CI) **	Reported incidences	Weighted mean (95%-CI) **	Reported incidences	Weighted mean (95%-CI) **
Revision surgery	0 [34], 9.0 [29], 14.9 [28]	11.5 (6.4–16.6)	27.7 [38], 40.9 [28], 45.5 [33], 54.0 [13]	42.4 (32.3–52.5)	0 [55], 0 [57], 0 [58], 2.9 [53], 9.0 [42], 12.0 [34], 47.0 [47], 66.7 [43]	23.6 (5.7–41.5)	6.4 [39], 10.0 [46], 11.1 [11]	8.5 (5.3–11.7)
Complication rate (total)	26.0 [29], 30.4 [12], 31.6 [45], 33.3 [34], 40.0 [41], 47.3 [28]	36.0 (28.2–43.8)	0 [12], 0 [45], 24.0 [40], 45.9 [13], 48.9 [38], 54.5 [28], 58.8 [55]	48.7 (38.8–58.6)	8.7 [57], 9.0 [42], 25.6 [30], 30.8 [55], 34.1 [12], 37.1 [53], 44.0 [34], 50.0 [36], 70.0 [47]	36.8 (22.5–51.1)	11.1 [11], 20.0 [46], 48.0 [40], 62.5 [12]	19.6 (0.9–38.3)
Patient satisfaction	69.2 [12]	69.2 (/)	0 [12], 41.4 [31], 90.0 [40], 92.3 [39]	61.7 (33.8–89.6)	73.3 [12], 80.0 [55], 82.6 [57], 83.0 [47], 92.3 [37]	81.7 (76.8–86.6)	42.9 [12], 67.0 [11], 80.0 [40], 88.9 [39]	78.2 (64.1–92.3)
Physician satisfaction	51.3 [12]	51.3 (/)	0 [12], 62.2 [13], 92.3 [39]	73.5 (49.4–97.6)	66.7 [12], 83.0 [47]	72.1 (57.0–87.2)	42.9 [12], 80.0 [11], 92.1 [39]	83.7 (68.2–99.2)

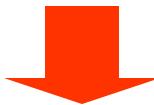
* All incidence rates are presented in percentages.

** 95%-CI: 95% confidence interval.

Review sistematica 37 studi, 2683 pts, 1635 autologo, 948 E/I

Quale metodo e timing migliore tra ricostruzione e RT?

- E/I post RT maggiori complicanze
- Autologo pre RT > chirurgia di revisione e fibrosi



- Ricostruzione immediata → E/I → RT
- Ricostruzione differita → RT → tessuto autologo

Berbers J Eur J Cancer 2014

Ricostruzione tessuto autologo rimuove tessuti danneggiati

Rozen WR, Ashton MW. Gland Surgery 2012

Timing RT/sostituzione espansore

- Ric immediata one vs two-stage > revisione e peggiore cosmesi
- Ricostruzione two-stage
sostituzione impianto prima RT > complicanze

Kronowitz SJ Plast Reconstr Surg 2012

- Sostituzione impianto pre RT vs post RT **Non diff SS**
- Sostituzione impianto dopo RT precoce vs tardiva (< vs > 4-6-12 mesi)

Lentz R et al Ann Plast Surg 2013

- Review sistematica

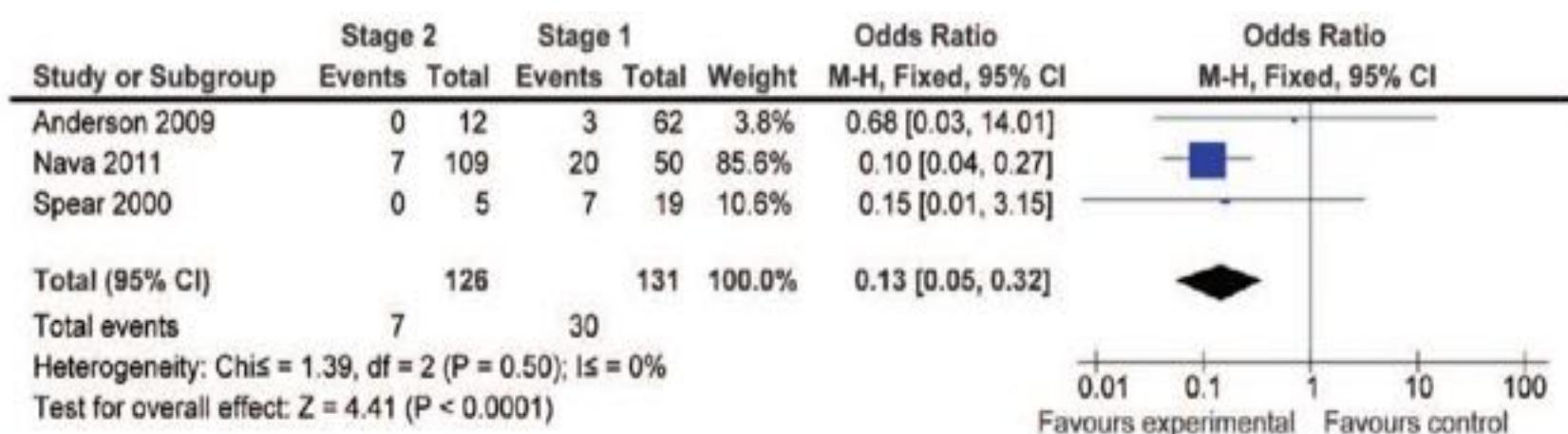


Fig. 5. Odds ratio forest plot of stage 2 (after implant) (5.6 percent) versus stage 1 (after expander) (22.9 percent) immediate breast reconstruction plus adjuvant radiotherapy for failure (prosthesis loss).

Lam TC et al. Plast Reconstr Surg 2013

Timing RT e sostituzione espansore/impianto

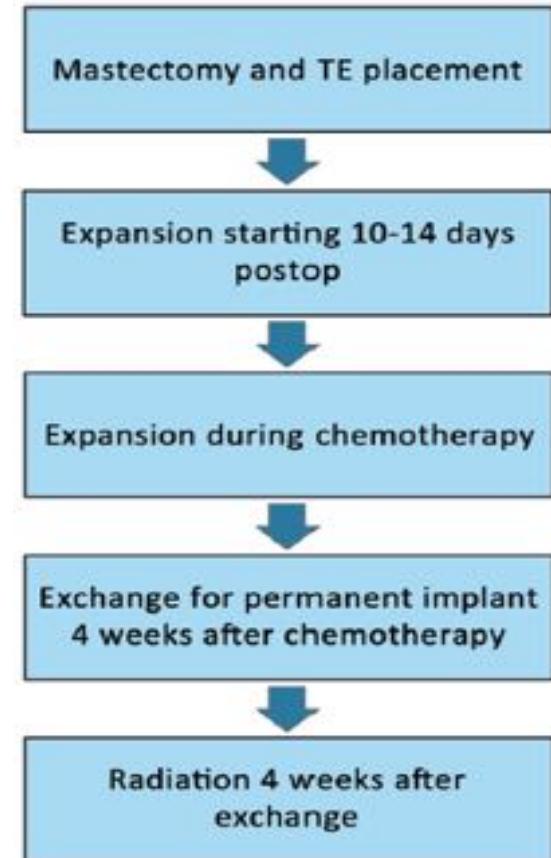
1415 pz ricostruzione protesica ± RT

	RT	no RT	
Fallimento impianto	9.1%	vs 0.5% p<0.01	
Contrat capsul IV grado	6.9%	vs 0.5% p<0.01	
Prob. Fallimento a 12 aa	17.5%	vs 2% p<0.01	
Cosmesi buona/eccell.	92%	vs 94.2%	

8 sett CT→RT

Cordeiro PG et al. Plast Reconstr Surg 2014

Algoritmo MSKCC

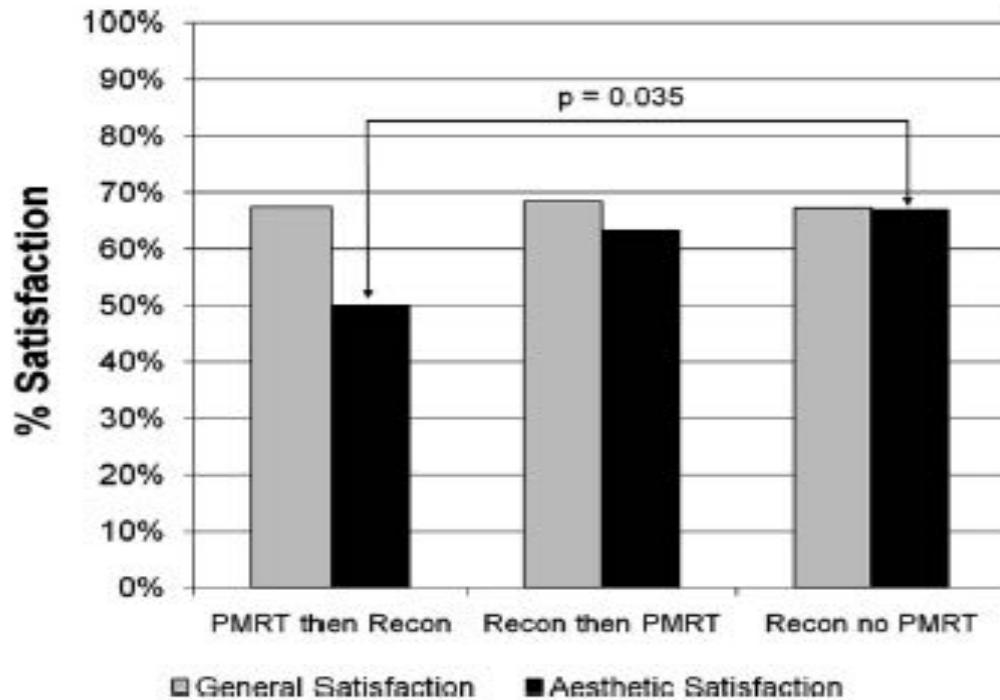


NB: RT con impianto permanente minor rischio fallimento 725 pz

Eriksson M et al. Breast Cancer Res Treat 2013

Soddisfazione pazienti e QoL

- Risultati generalmente buoni ≠ modalità e timing RT



Da Lee BT et al. Ann Plast Surg 2010

FIGURE 2. Patient satisfaction.

Adesiyun TA et al. Int J Radiat Oncol Biol Phys 2011
Tsoi B et al. J Am Coll Surg 2014

- > soddisfazione per protesi silicone vs salina

McCarthy CM et al. Cancer 2010

Ricostruzione E/I: QoL e soddisfazione pazienti

Table 5 Postoperative PROMs after immediate implant-based breast reconstruction in the three groups using five scales of the Breast-Q®

	No RT (n = 274)	Prior RT (n = 35)	Postoperative RT (n = 197)	RT versus no RT <i>p</i> value	Prior versus postoperative RT <i>p</i> value
Satisfaction with breast/s	57.6 (16.7)	48.6 (15.1)	50.9 (15.8)	0.000**	0.414
Satisfaction with overall outcome	70.3 (18.6)	63.1 (18.5)	63.8 (18.9)	0.000**	0.905
Psychosocial well-being	70.9 (23.0)	64.6 (21.3)	63.9 (21.6)	0.001**	0.974
Sexual well-being	54.6 (25.5)	45.6 (25.6)	48.2 (22.9)	0.002**	0.503
Physical well-being	78.3 (16.8)	71.7 (14.6)	75.1 (15.7)	0.005**	0.137

Numbers (N) represent individual patients. RT radiotherapy. Mean (SD)

* *p* value <0.05, ** *p* value <0.01

Eriksson M et al. Breast Cancer Res Treat 2013



TABLE 4 BREAST-Q scores in patients with postmastectomy radiation compared with nonirradiated patients

BREAST-Q scale	Mean BREAST-Q scores (SD)		Mean score difference	<i>p</i> value
	Nonirradiated group (n = 414)	Postmastectomy radiation group ^a (n = 172)		
Satisfaction with breasts	64.0 (21.7)	57.0 (21.8)	7.0	<0.01
Satisfaction with outcome	71.4 (22.7)	64.9 (24.0)	6.5	<0.01
Psychosocial well-being	70.9 (20.5)	65.2 (21.4)	5.7	<0.01
Sexual well-being	52.3 (21.7)	45.4 (20.7)	6.9	<0.01
Physical well-being: chest and upper body	75.1 (17.0)	71.7 (17.8)	3.4	0.01

Unadjusted scores

^a Includes only patients with radiation to the tissue expander or the permanent implant

Modalità di trattamento RT

- Tecnica standard buona copertura bersagli, rispetto OAR
- Protesi, espansore o valvola metallica non interferenza con distribuzione di dose
- RT su IMN → > dose polmone e cuore

Sensus-Konefka E et al Cancer Treat Rev 30:671-682, 2004

Moni J et al. Med Dosim 2004

Thompson RCA, Morgan AM. Med Phys 2005

Damast S et al. Int J Radiat Oncol Biol Phys 2006

Chen SA et al. Int J Radiat Oncol Biol Phys 2013

Chang EI et al Plast Reconstr Surg 131:1-8, 2013

Ohri N et al Int J Radiat Oncol Biol Phys 2012

Ho AY et al Med Dos 2014

Liljegren A et al. Radiat Oncol 9:14-23, 2014

- IMRT

Jung AL et al J Med Im Radiat Oncol 2013

Koutcher L et al. Radiother Oncol 2010

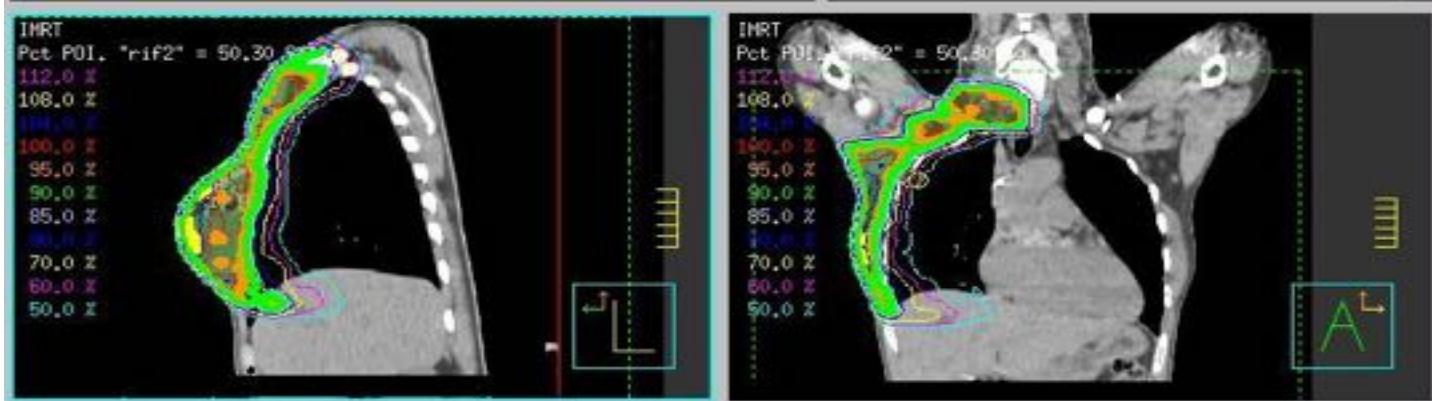
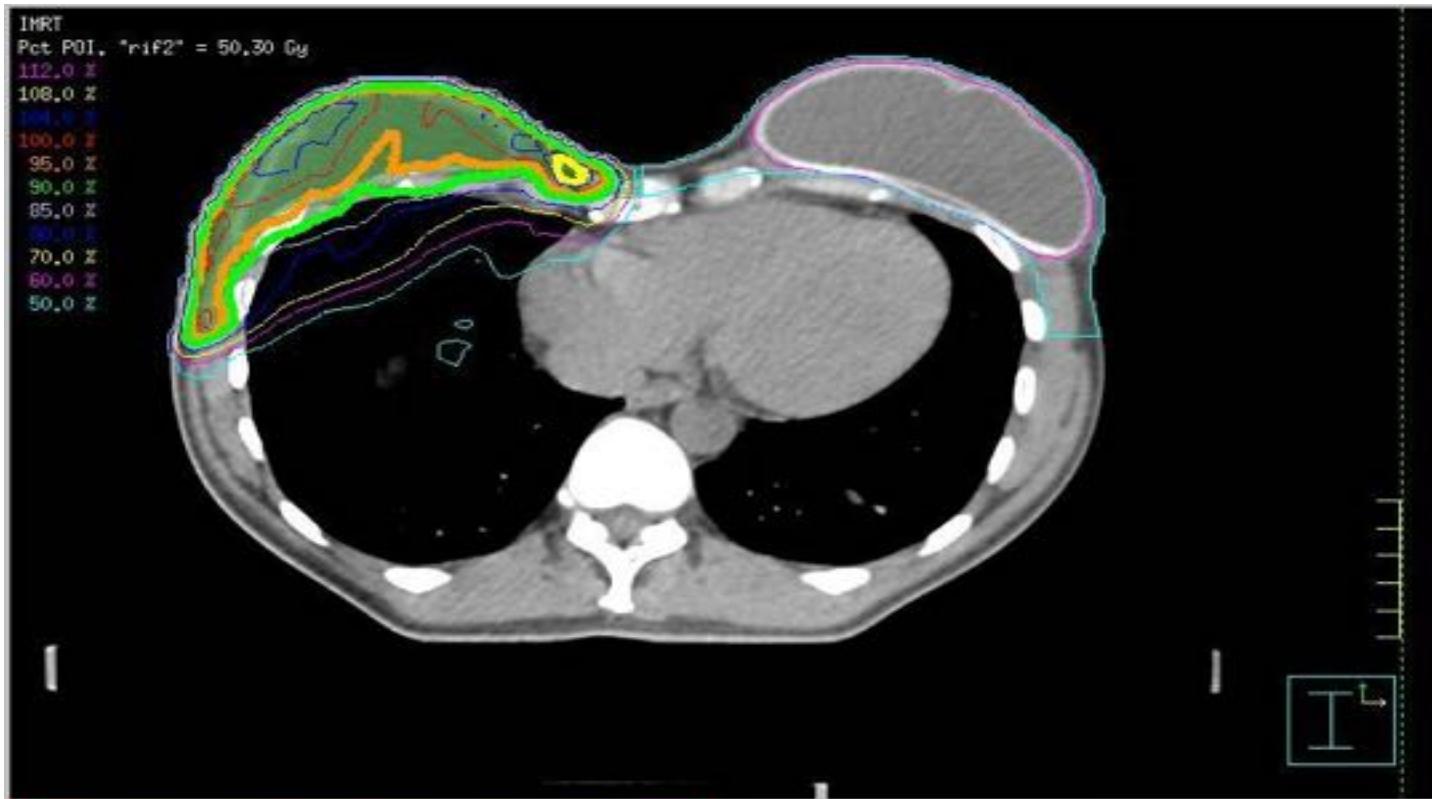
- HT → completa copertura target < alte dosi OAR, ma > basse dosi tessuti sani...

Massabeau C et al. Med Dosim 2012

- IMPT ...

Jimenez RB et al Radiother Oncol 2013

IMRT parete toracica e drenaggi dopo ricostruzione con E/I



Conclusioni

- ✓ Interferenza RT/ricostruzione è indipendente da tipo di ricostruzione e timing
- ✓ Tipo ricostruzione/Timing RT:
 - E/I immediata → RT,
 - RT → autologo differita
 - RT impianto vs espansore < complicate
- ✓ Modalità trattamento RT in evoluzione → IMRT
- ✓ Selezione/informazione pazienti ≠ ricostruzioni
- ✓ Training operatore E/I silicone, no ADM, tipo di lembo
- ✓ Valutazione QoL, cosmesi e soddisfazione pz

Grazie dell'attenzione

Complicanze precoci/tardive

Precoci:

- Infezione/infiammazione
- Ematoma, Sieroma
- Necrosi
- Rigetto

Tardive:

- Fibrosi
- Contrattura capsulare
- Estrusione, dislocazione
- Morfologia alterata
- Dolore