Current perspectives on radiation therapy in autologous and prosthetic breast

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DBCG 82 b & c

1152 pLN(+), 8 or more nodes removed
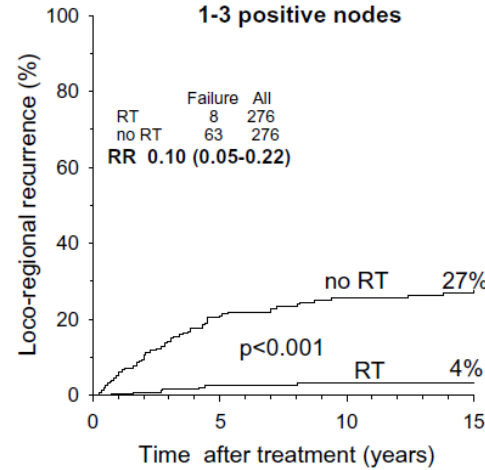
Systemic therapy
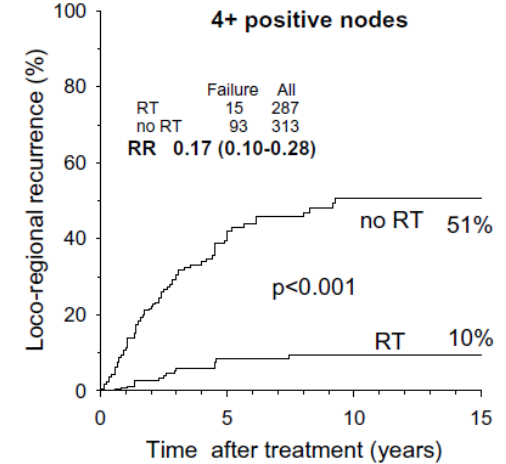   CMF 8-9cycles
      or TAM 30mg for 48 weeks

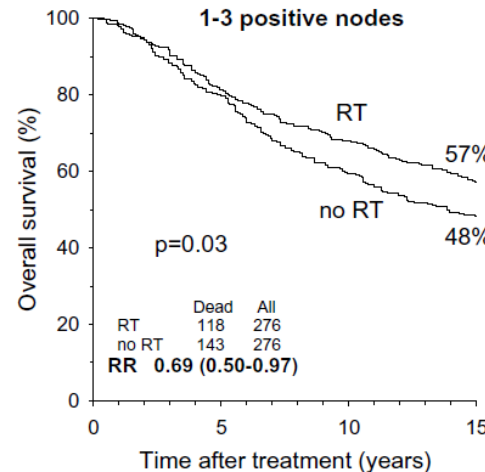Radiotherapy
      48-50 Gy in 22-35 frs
      chest wall, RNI
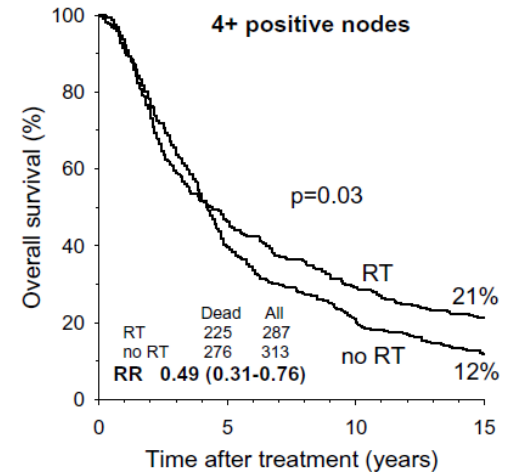
Overgaard et al Radiot Oncol 2007

British Columbia Randomized trial

Breast cancer-free survival
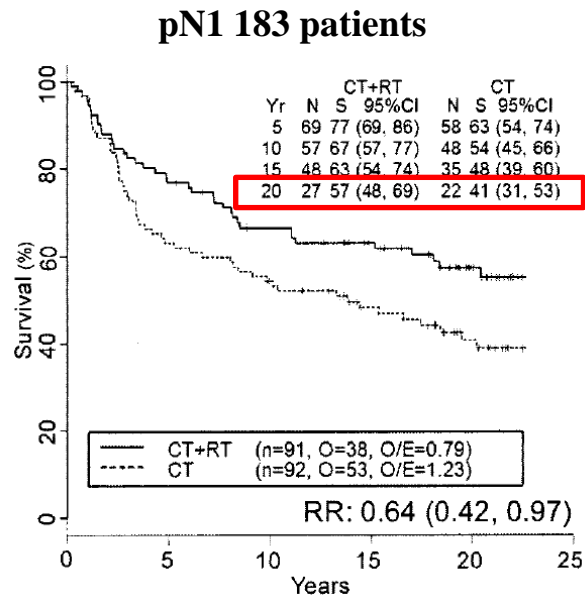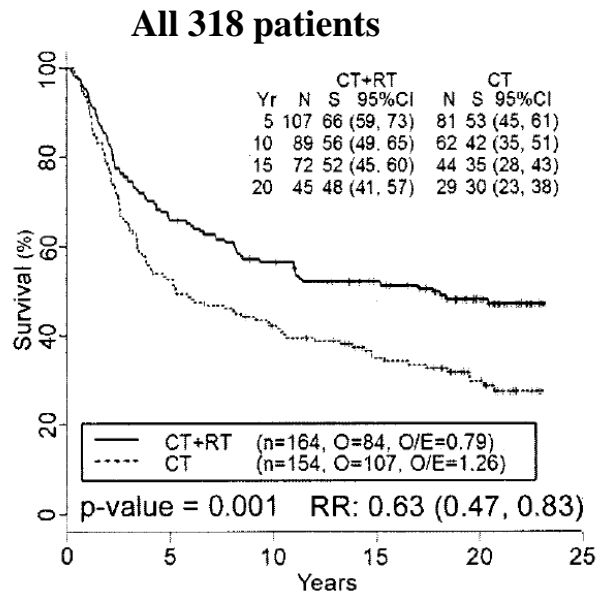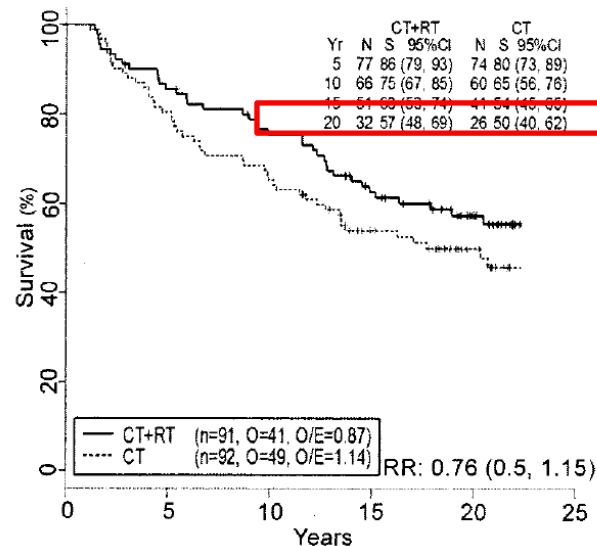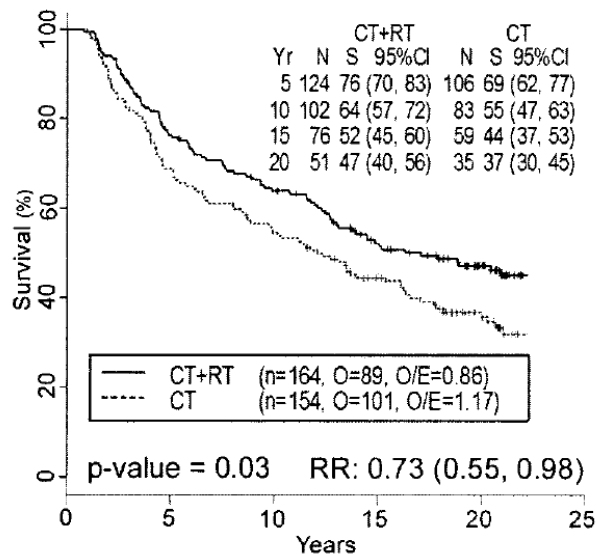
Meta-analysis for 8135 women in 22 trials

700 pN0 women with Mast+AD

A Locoregional recurrence first

log-rank 2p>0·1; NS

RT 3·0%
No RT 1·6%
1·9
1·2

B Any first recurrence

10-year loss 1·3% (SE 3·3)
RR 1·06 (95% CI 0·76–1·48)
log-rank 2p>0·1; NS

RT 22·4%
No RT 21·1%
15·5
13·3

C Breast cancer mortality

20-year loss 2·2% (SE 3·6)
RR 1·18 (95% CI 0·89–1·55)
log-rank 2p>0·1; NS

RT 28·8%
No RT 26·6%
25·9
23·9
18·4
18·3
11·0
10·6
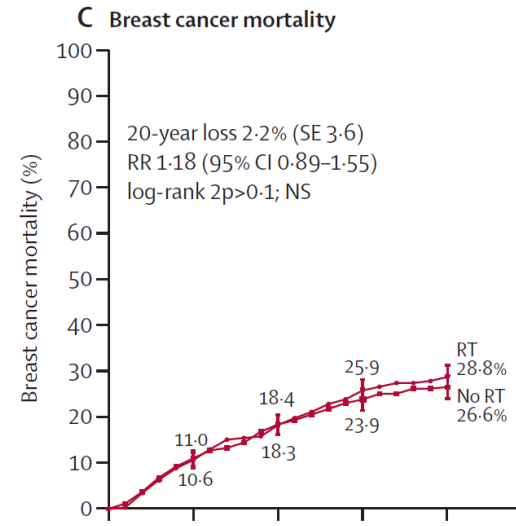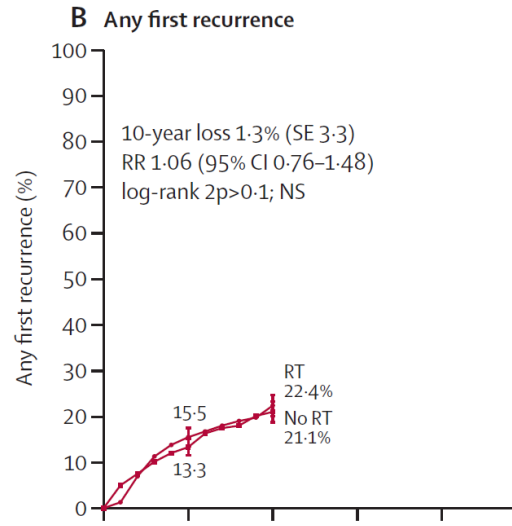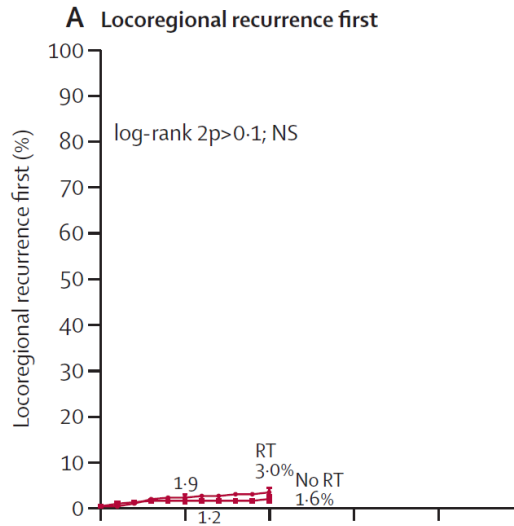
3131 pN+ women with Mast+AD

D Locoregional recurrence first

log-rank 2p<0·00001

No RT 26·0%
21·3
RT 8·1%
6·6

E Any first recurrence

No RT 62·5%
52·4
RT 51·9%
43·0

10-year gain 10·6% (SE 2·0)
RR 0·75 (95% CI 0·67–0·83)
log-rank 2p<0·00001

F Breast cancer mortality

No RT 66·4%
62·6
54·1
RT 58·3%
55·4
48·0
37·2
33·9

20-year gain 8·1% (SE 2·0)
RR 0·84 (95% CI 0·76–0·94)
log-rank 2p=0·001

Years

EBCTCG Lancet 2014
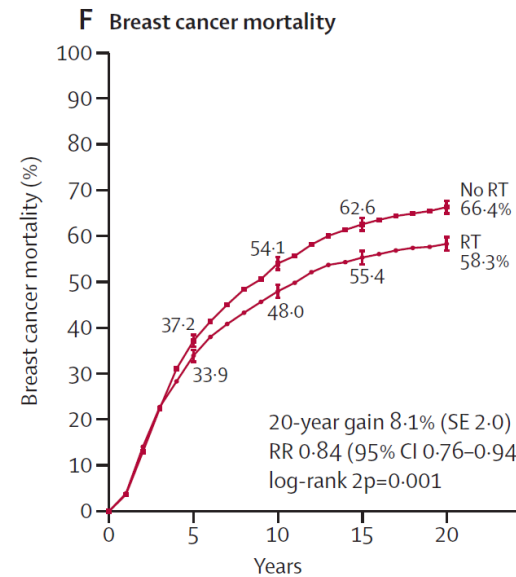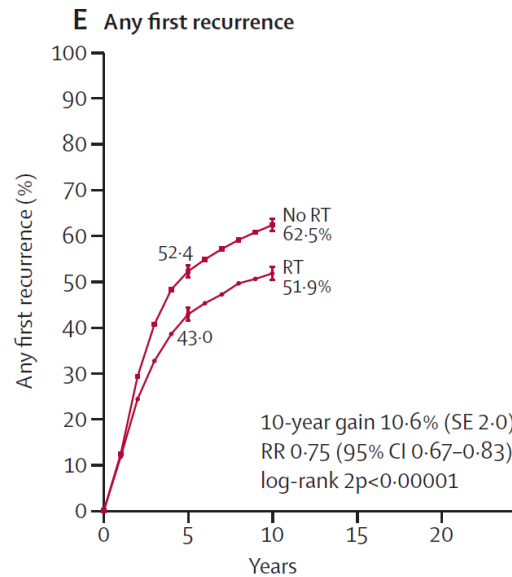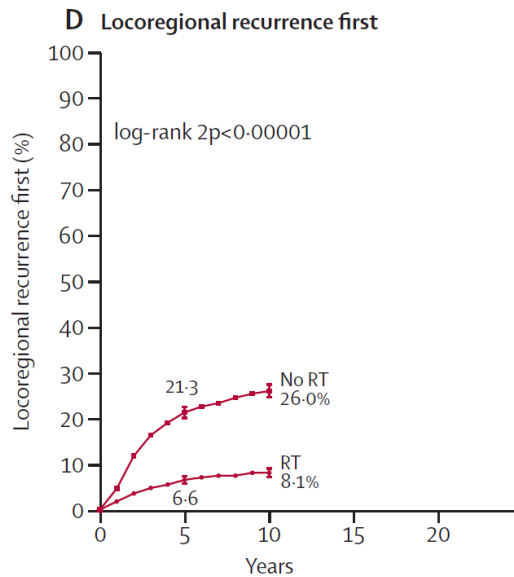
- breast reconstruction: increase QOL
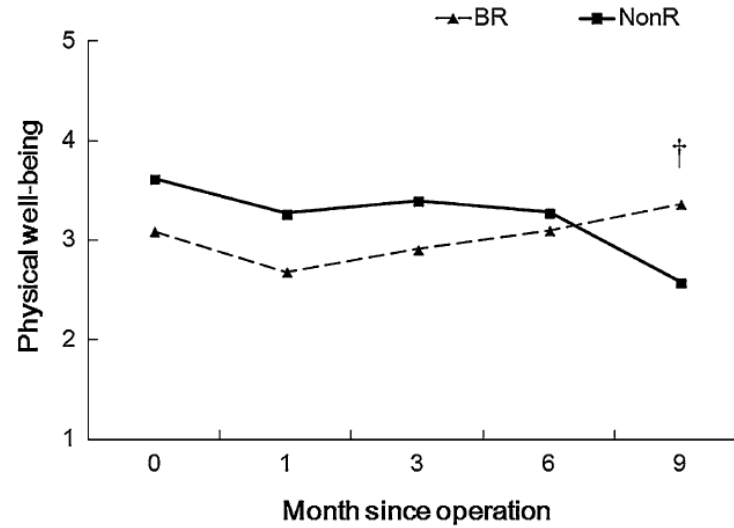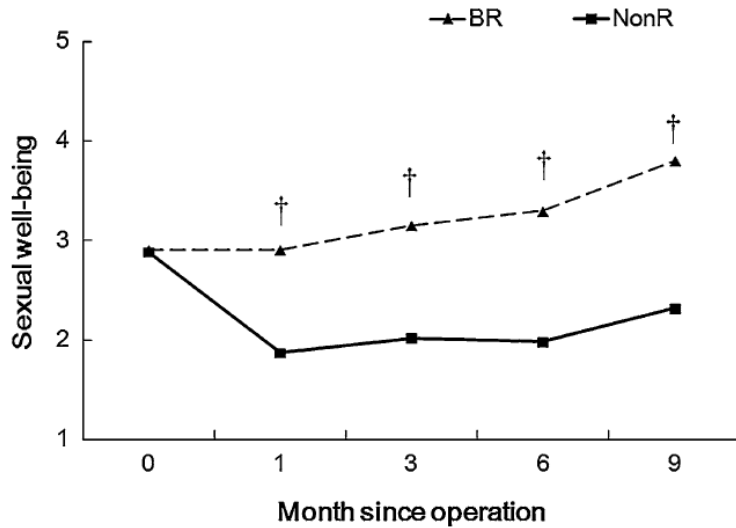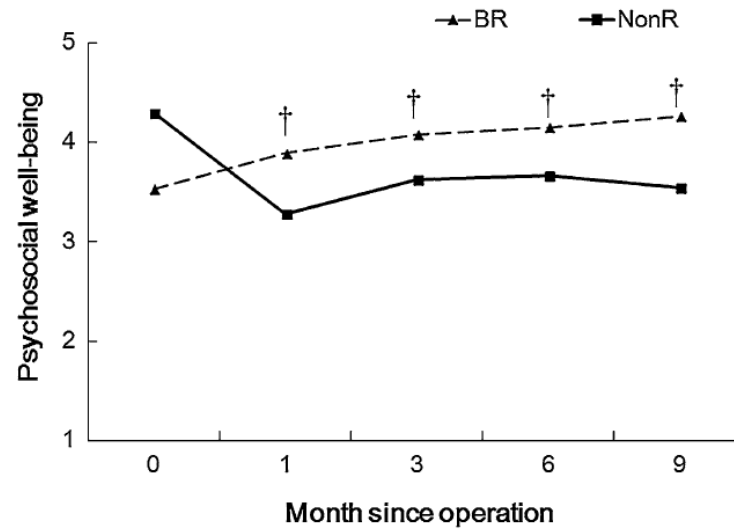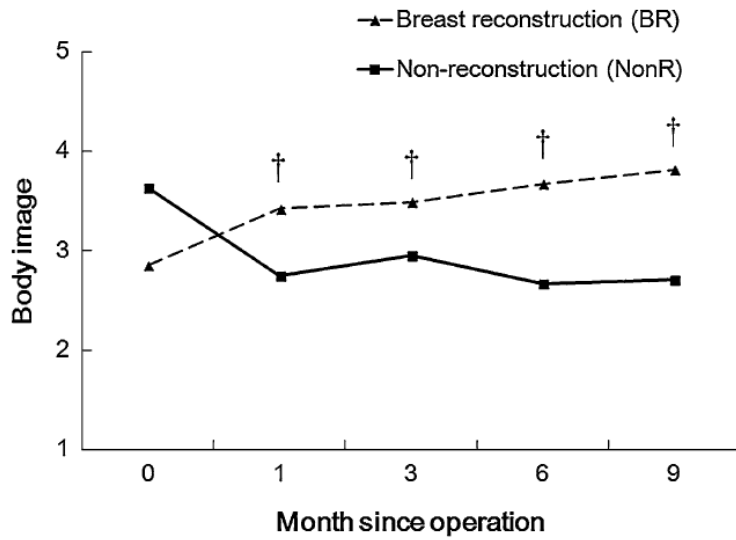
Issues of PMRT with reconstruction

1. Method
    - prosthetic reconstruction
    - autologous reconstruction

2. Timing
    - immediate
    - delayed

3. Implant volume
    - inflation
    - deflation

Radiation induced skin reaction

- acute phase: inflammatory reaction

      swelling

      edema

      erythema

      desquamation

      ulceration

-chronic phase: fibrosis

      skin retraction

      induration

      pain

      restricted movement

Factors to PMRT and reconstruction outcomes

- Radiotherapy dose

- Length of treatment

- Time separating reconstructive surgery from radiation

- Method of reconstruction

PMRT effects in reconstruction

- in implants patients

      capsular contracture

      infection

      loss of prostheses

- in autologous patients

      fibrosis

      distortion

      volume loss

      fat necrosis

Prosthetic reconstruction

Failure rate: 11% (83/754)

without RT: 6% (22/386)

prior RT (previous RT): 25% (16/64)

postop RT (RT after IBR): 15% (45/304)

Table 3 Number of unplanned reoperations after implant-based immediate breast reconstruction per group

Radiotherapy (RT)	Number of unplanned reoperation, n (%)						
	0	1	2	3	4	5	6
No RT	215 (56.1)	141 (36.8)	19 (5.0)	6 (1.6)	2 (0.5)	0	0
Prior RT	22 (34.4)	31 (48.4)	11 (17.2)	0	0	0	0
Postoperative RT	124 (40.9)	136 (44.9)	30 (9.9)	10 (3.3)	2 (0.7)	0	1 (0.3)

PROMs	No RT (n = 274)	Prior RT (n = 35)	Postoperative RT (n = 197)	RT versus no RT p value	Prior versus postoperative RT p 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

Prosthetic reconstruction

- Two mechanism

1. single-stage implant

2. two-stage implant: tissue expander prior to permanent implant

Breast Cancer Diagnosis — Mastectomy/ Expander Placement — Expander-Implant Exchange Before PMRT — Radiation — Expander-Implant Exchange After PMRT
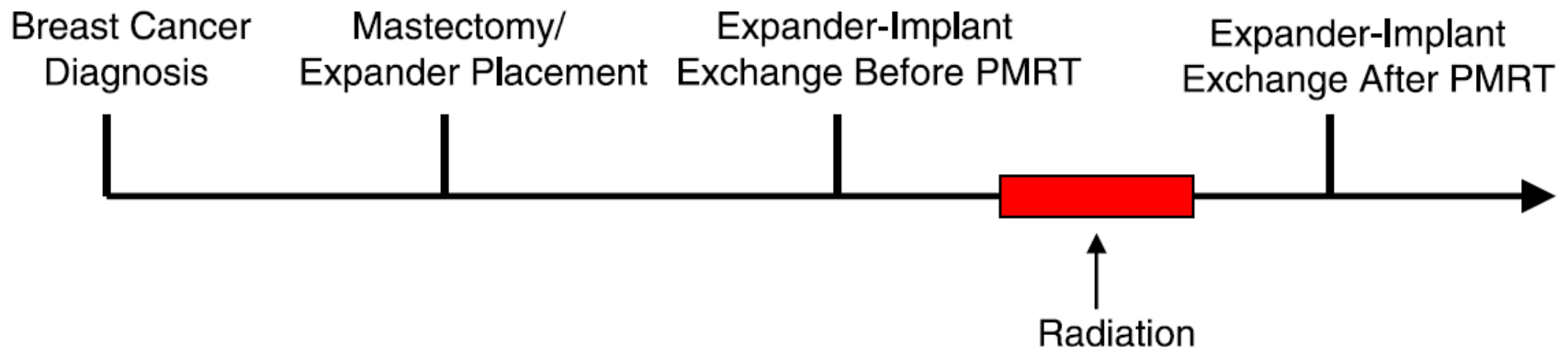
Prosthetic reconstruction

Reference	No	Mean FU (mo)	RT applied	RT Timing	Outcomes
Fowble et al (2015)	86 13	45.6 45.6	TE PI	- -	Failure:19.8% Failure: 7.7%
Cordeiro et al (2015)	94 210	30.1 40.3	TE PI	6mo 4wks	Failure:18.1%, contracture:17.1% Failure:12.4%, contracture:50.9%
Collier et al (2014)	32 22	16.3 25.0	TE PI	4.6mo 1.6mo	Failure:6.3%, infection:9.4% Failure:4.5%, infection:9.1%
Lentz et al (2013)	34 22	27.3 46.0	TE PI	- -	Failure:20.6%, contracture:11.8% Failure:13.6%, contracture:40.9%
Nava et al (2011)	50 109	50 50	TE PI	>6mo 3wks	Failure:40%, contracture:53.3% Failure:6.4%, contracture:57.8%
Anderson et al (2009)	62 12	36 23	TE PI	- -	Failure:4.8%, infection:4.8% Failure:0%, infection:0%
Overall outcomes			TE PI		Failure: 5-40%, Contracture:12-53% Infection: 5-9% Failure: 0-14%, Contracture: 21-58% Infection: 0-9%

Aesthetic outcomes in RT to TE or PI

- Aesthetic outcome: mixed results

	PMRT after TE	PMRT after PI
Good or better	36.1-100%	80-92.4%

Patients opinion	PMRT after TE	PMRT after PI	P-value	Control
Cordiero et al (2015) excellent/good	75%	67.6%	<0.01	
Nava et al (2011) good	46.2%	52.2%	0.04	68.1%
Anderson et al (2009) excellent/good	90%	80%	0.22	

Timing of expander-implant exchange after PMRT

- UCSF, 88 pts
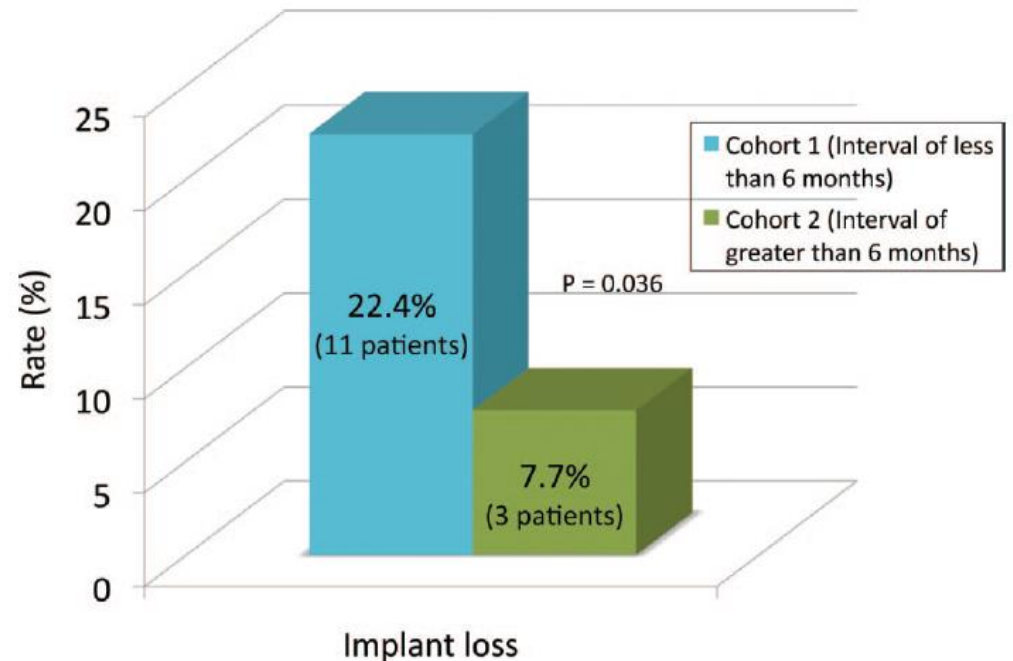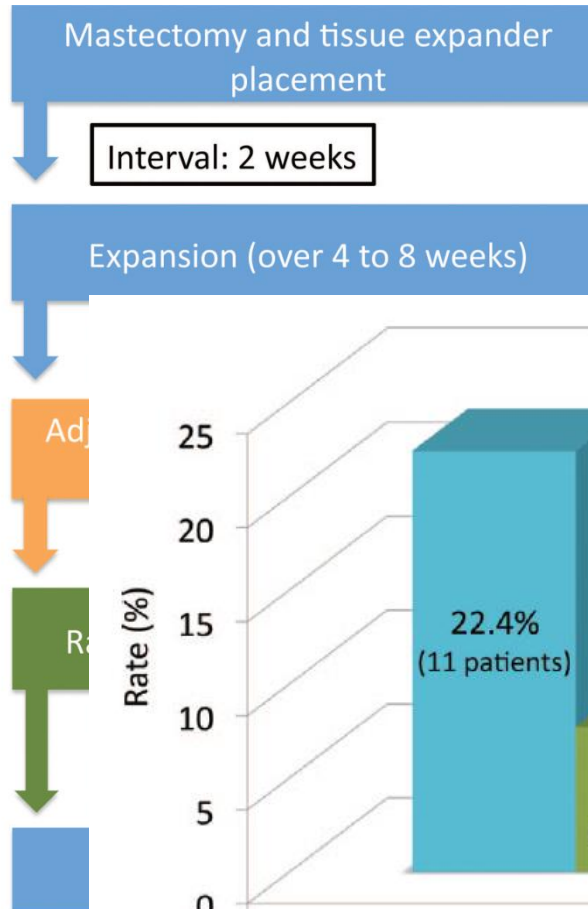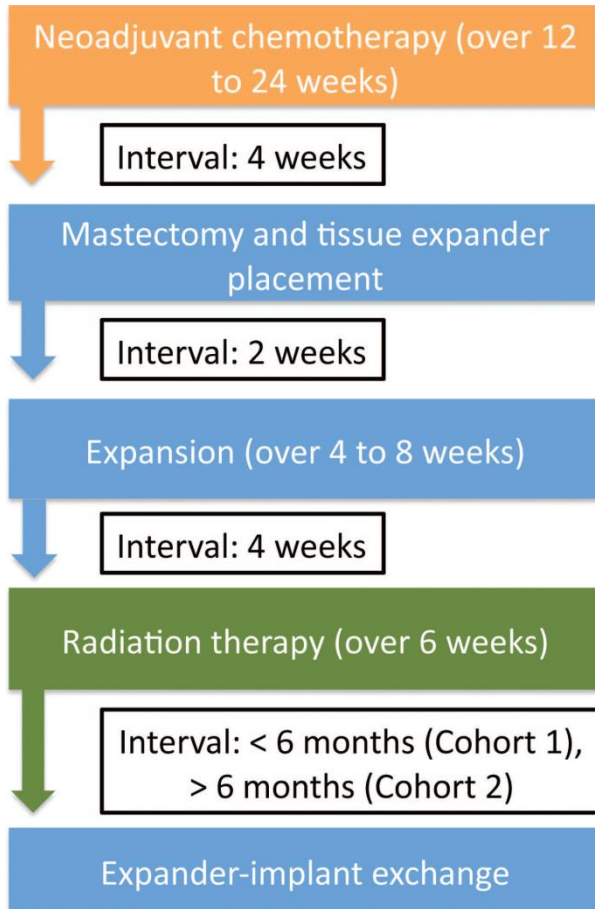
Timing of expander-implant exchange after PMRT

- Yale university, 34 pts

Breast Cancer Diagnosis — Mastectomy/Expander Placement — Radiation — Expander-Implant Exchange

x

Exchange < 4 months After PMRT

Exchange > 4 months After PMRT

Overall Complications p=0.487 — Early Exchange 40.00%, Late Exchange 57.10%

Failure p=0.672 — Early Exchange 25.00%, Late Exchange 14.30%
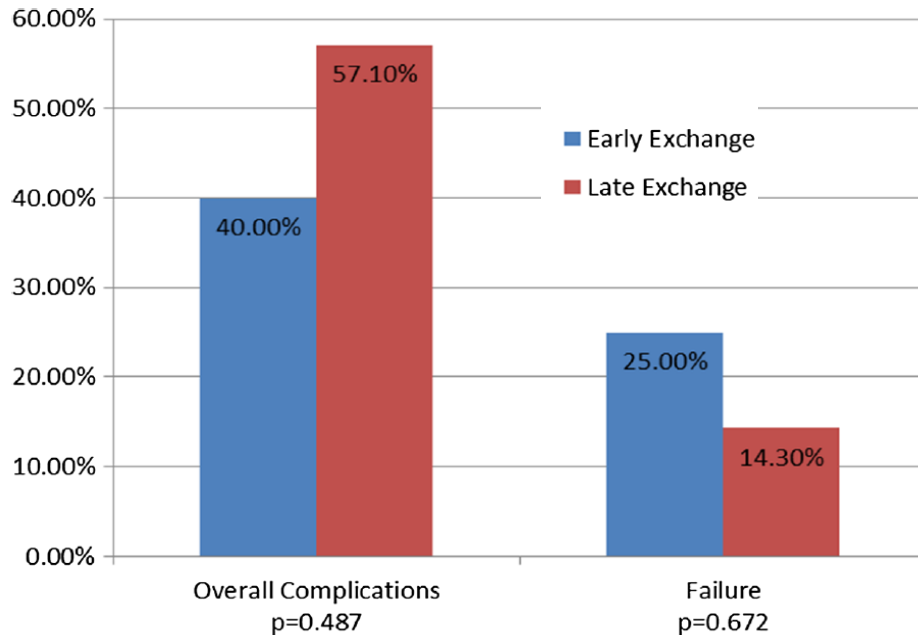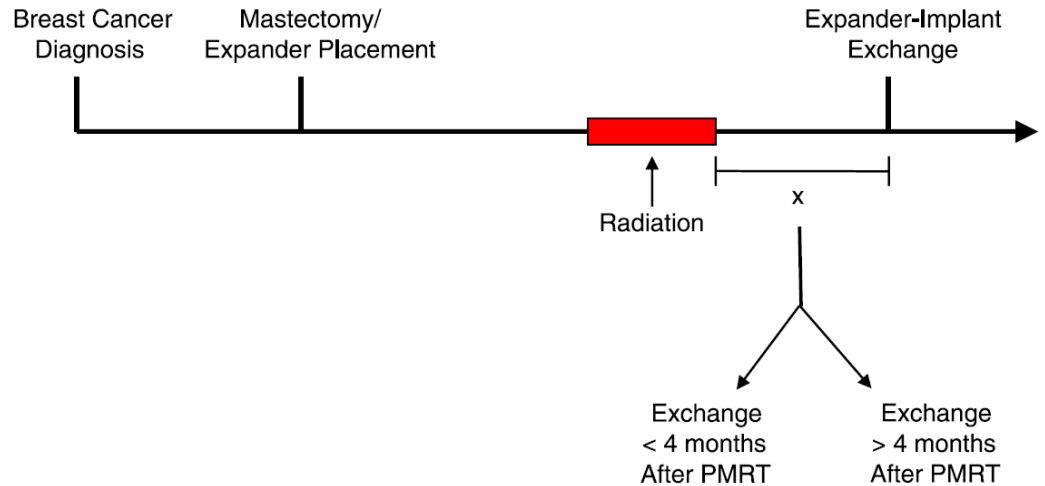
TABLE 7. Indications for Surgery/Hospitalization Across Groups That Underwent Exchange After PMRT

	Early Exchange (n = 20)		Late Exchange (n = 14)		
	n	%	n	%	*P*
Infection	6	30.0	2	14.3	0.42
Wound dehiscence/extrusion	3	15.0	2	14.3	1
Seroma	1	5.0	0	0	1
Hematoma	0	0	2	14.3	0.16
Capsular contracture	1	5.0	3	21.4	0.28

Systemic review and Pooled analysis

- 2000-2015, Pubmed/MEDLINE database

- Breast reconstruction in the setting of PMRT and adj chemotherapy

- 56 manuscripts: PMRT

  11 manuscripts: chemotherapy

Characteristics	Value
No. of patients	3605
Mean age ± SD, yr	46.9 ± 2.2
Mean BMI ± SD, kg/m^2	24.9 ± 0.9
Method of Reconstruction	
TE/I, n (%)	3192 (87.3)
DTI, n (%)	28 (0.8)
LD combined with implant, n (%)	64 (1.8)
Not specified, n (%)	373 (10.1)
Timing of PMRT	
Applied to TE, n (%)	1951 (53.3)
Applied to PI, n (%)	1116 (30.5)
Not specified, n (%)	590 (16.1)
Adj. Chemotherapy, n (%)	1623 (70.8)
Mean follow-up ± SD, mo	38.8 ± 12.6

Characteristics	Value
No. of patients	1832
Mean age ± SD	48.1 ± 3.4
Mean BMI ± SD	27.6 ± 1.3
Timing of definitive reconstruction	
Immediate, n (%)	655 (34.9)
Delayed, n (%)	833 (44.3)
Delayed-immediate, n (%)	195 (10.4)
Not specified, n (%)	195 (10.4)
Method of reconstruction	
TRAM, n (%)	1030 (54.8)
DIEP, n (%)	367 (19.5)
LD, n (%)	31 (1.7)
Not specified/other, n (%)	450 (24.0)
Timing of PMRT	
Before definitive reconstruction, n (%)	1037 (55.2)
After definitive reconstruction, n (%)	841 (44.8)
Adj. Chemotherapy, n (%)	266 (68.0)
Mean follow-up ± SD, mo	33.5 ± 14.9

Systemic review and Pooled analysis

- 2000-2015, Pubmed/MEDLINE database

Complication	Device-based, % (n)	Autologous, % (n)	P-value
Hematoma	2.75 (23)	6.09 (21)	0.02
Seroma	5.95 (52)	8.00 (34)	0.02
Infection	13.51 (141)	5.79 (42)	<0.0001
Wound dehiscence/ delayed wound healing	5.77 (19)	12.89 (46)	0.001
Capsular Contraction[a]	38.02 (511)	—	—
Flap fibrosis	—	30.32 (104)	—
Mastectomy Flap Necrosis	10.49 (82)	5.01 (20)	0.03
Fat necrosis	—	15.15 (137)	—
Partial Flap Loss	—	4.31 (35)	—
Exposure/extrusion	5.19 (46)	—	—
Reoperations	36.95 (470)	16.58 (124)	<0.0001
Reconstructive Failure[b]	16.84 (560)	1.59 (19)	<0.0001
Total Complication Rate	41.32 (380)	30.91 (361)	<0.0001

Autologous reconstruction

- Harvard Medial School, 199 patients

Complications	Radiation (n = 100) Number (%)	No Radiation (n = 99) Number (%)	P
Total flap loss	1 (1.0)	0	1.0000
Partial flap loss	2 (2.0)	1 (1.0)	1.0000
Vascular thrombosis*	4 (4.0)	4 (4.0)	1.0000
Fat necrosis	12 (12.0)	11 (11.1)	0.8445
Wound dehiscence	11 (11.0)	3 (3.0)	0.0489
Infection	7 (7.0)	1 (1.0)	0.0649
Seroma	3 (3.0)	0	0.2462
Total	40 (40.0)	20 (20.2)	0.0023

Autologous reconstruction

Reference	No	Mean FU (mo)	Timing of reconstruction	PMRT timing	Outcomes
Patel et al (2013)	74 118	33.6 38.4	Two-stage Delayed	After TE Before recon	Reoperation: 9.6%, flap loss: 4.1% Reoperation:11.9%, flap loss:2.5%
Carlson et al (2008)	25 15	- -	Immediate Delayed	After recon Before recon	fat necrosis:32%, remedial surgery: 12% fat necrosis: 13.3%, remedial surgery: 0%
Tran et al (2001)	32 70	36 60	Immediate Delayed	After recon Before recon	fat necrosis: 43.8%, volume loss:87.5% fat necrosis: 8.6%, volume loss: 0%

Timing of autologous reconstruction after PMRT

- Harvard Medial School, 199 patients

Complications	0–12 mo (n = 51) Number (%)	>12 mo (n = 49) Number (%)	P
Total flap loss	0	1 (2.0)	0.4900
Partial flap loss	2 (3.9)	0	0.4952
Vascular thrombosis*	3 (5.8)	1 (2.0)	0.6176
Fat necrosis	5 (9.8)	7 (14.3)	0.5501
Wound dehiscence	7 (13.7)	4 (8.2)	0.5256
Infection	5 (9.8)	3 (6.1)	0.7155
Seroma	0	2 (4.1)	0.4950
Total	22 (43.1)	18 (36.7)	0.5135

Complications	<6 mo (n = 17) Number (%)	>6 mo (n = 83) Number (%)	P
Total flap loss	0	1 (1.2)	1.0000
Partial flap loss	0	2 (2.4)	1.0000
Vascular thrombosis*	1 (4.2)	3 (3.6)	0.5314
Fat necrosis	1 (4.2)	11 (13.3)	0.6851
Wound dehiscence	2 (8.3)	9 (10.8)	1.0000
Infection	2 (8.3)	5 (6.0)	0.3398
Seroma	1 (4.2)	2 (2.4)	0.4318
Total	7 (29.2)	33 (39.8)	1.0000

Ann Plast Surg 2012:69
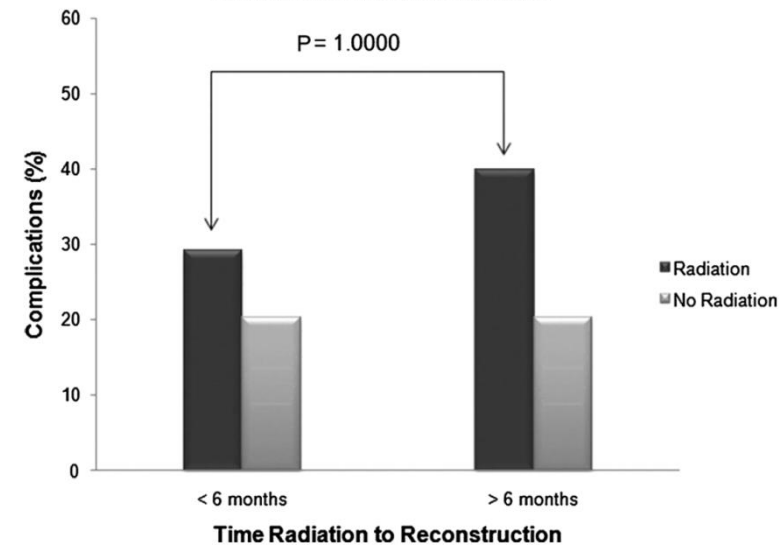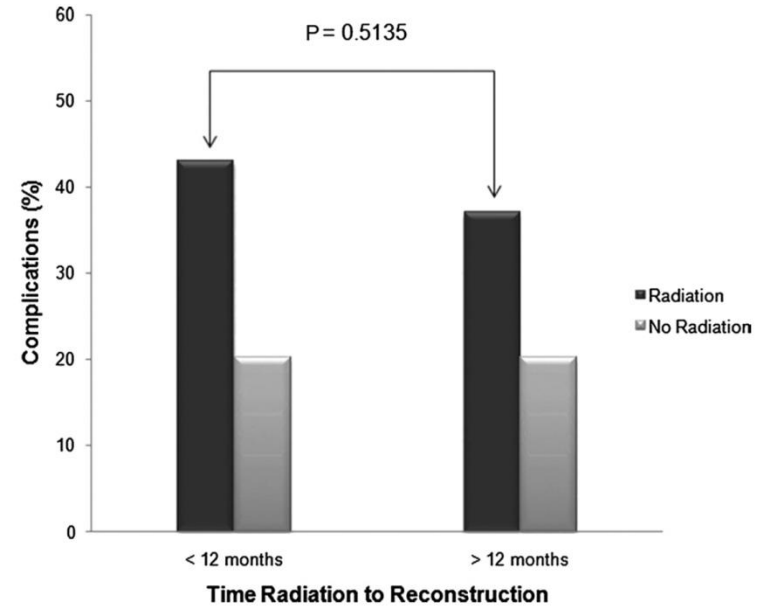
# Timing of autologous reconstruction after PMRT

- MDACC, 189 patients

  group I: reconstruction less than 12 months after PMRT
  group II: reconstruction 12 months or more after PMRT

	Group I (%)	Group II (%)	p^*
No. of patients	82	107	
Complication			
Total flap loss	5 (6)	0 (0)	0.014
Partial flap loss	5 (6)	9 (8)	0.590
Microvascular thrombosis	7 (9)	4 (4)	0.214
Reoperation <30 days	12 (15)	5 (5)	0.022
Wound dehiscence	10 (12)	12 (11)	0.835
Fat necrosis	5 (6)	10 (9)	0.589
Infection	3 (4)	1 (1)	0.631

Timing of autologous reconstruction after PMRT

- Georgetown University, 152 patients
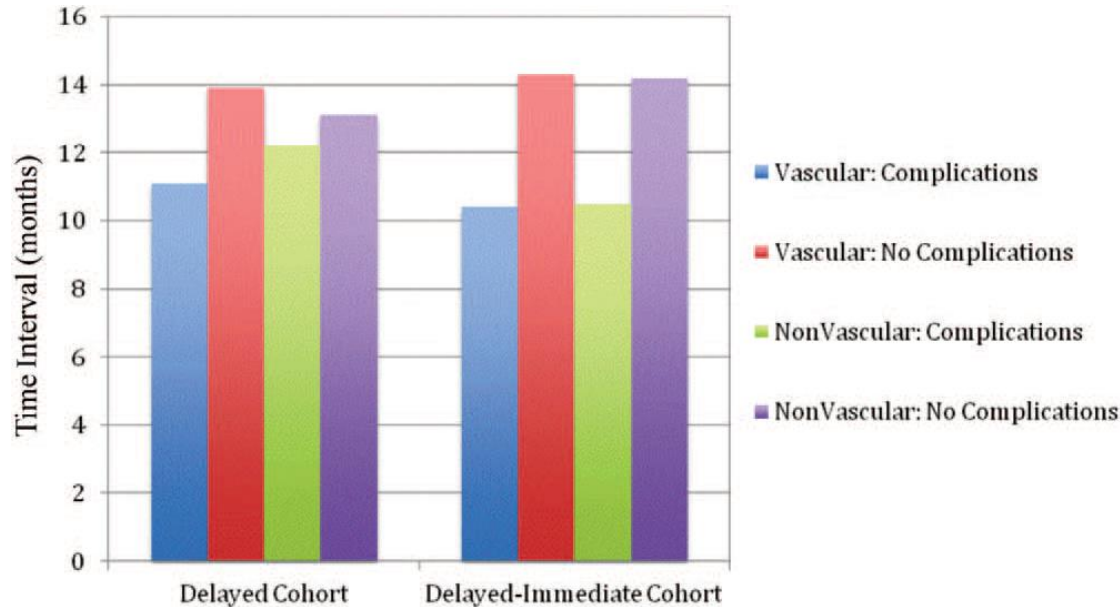
	before 12months	after 12 months	p-value
overall complication	34.0%	13.9%	0.002
delayed-immediate	37.5%	8%	0.04
delayed	38.5%	25%	0.37

Aesthetic outcomes in RT and AR

- Aesthetic outcome: mixed results

	Immediate recon + PMRT	PMRT + delayed recon
(+) aesthetic outcomes	70-85%	59.3%
Aesthetic means	2.6-3.0 (4 point scale)	2.94 (5 point scale)

Lee et al (2010)	Recon->PMRT	PMRT-> recon	Control
general satisfaction	75%	74.1%	74.1%
aesthetic satisfaction	66.7%	59.3%	75.7%

TE and PMRT: deflation vs. inflation
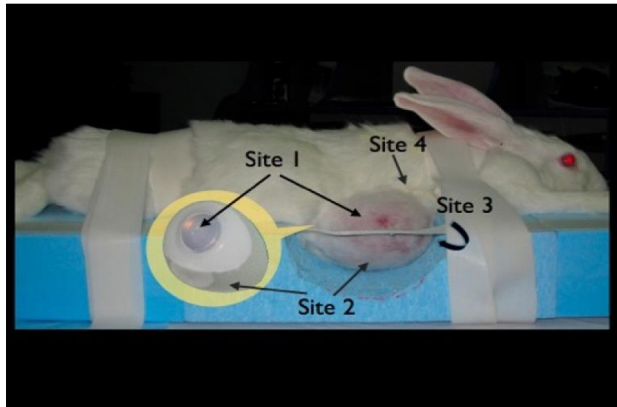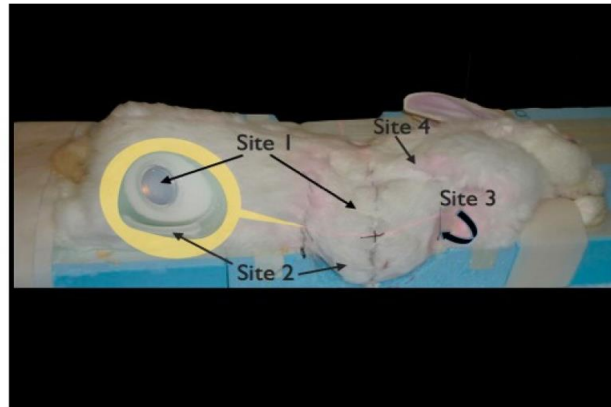
deflation

inflation
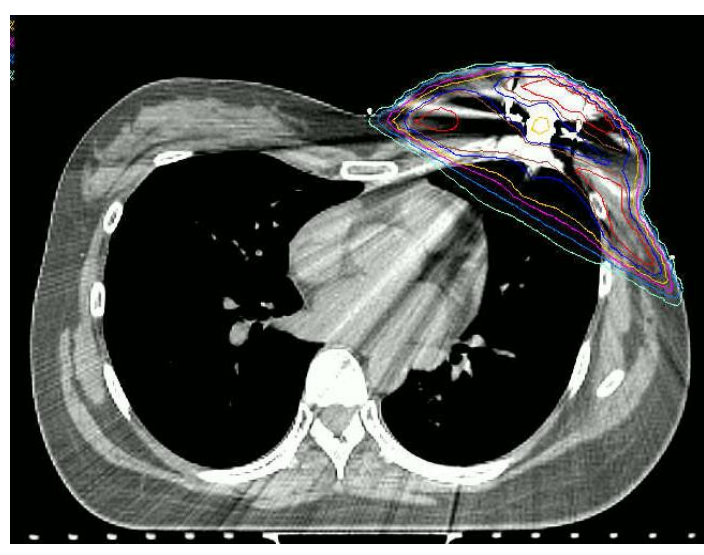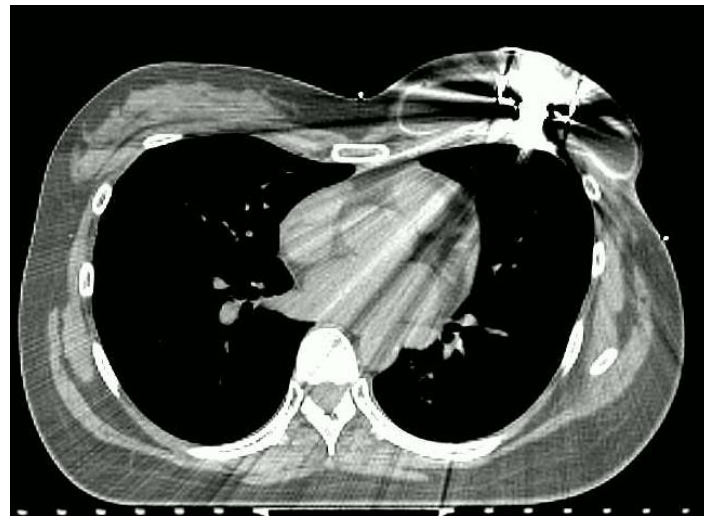
TE and PMRT: deflation vs. inflation

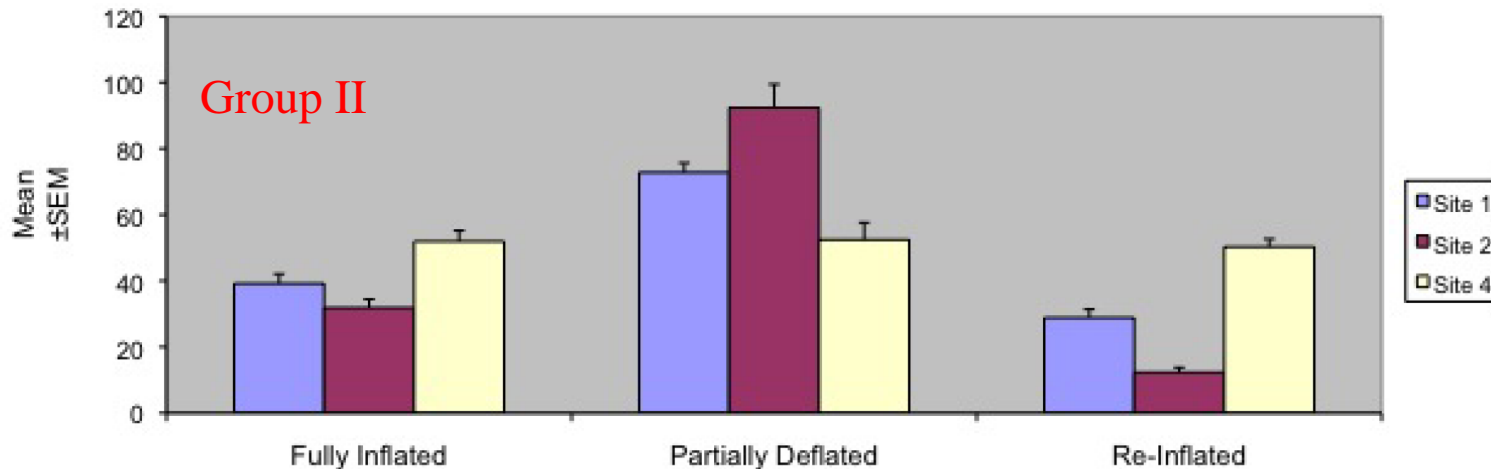- Istanbul university, in vivo, 18 rabbits

Group I   Group II

Group I: fully inflated
Group II: partially deflated
Group III: control, no radiotherapy

Skin Blood Flow Assesed by Laser Doppler (ml/min/100 g)

Group II

TE and PMRT: deflation vs. inflation

- Istanbul university, in vivo, 18 rabbits

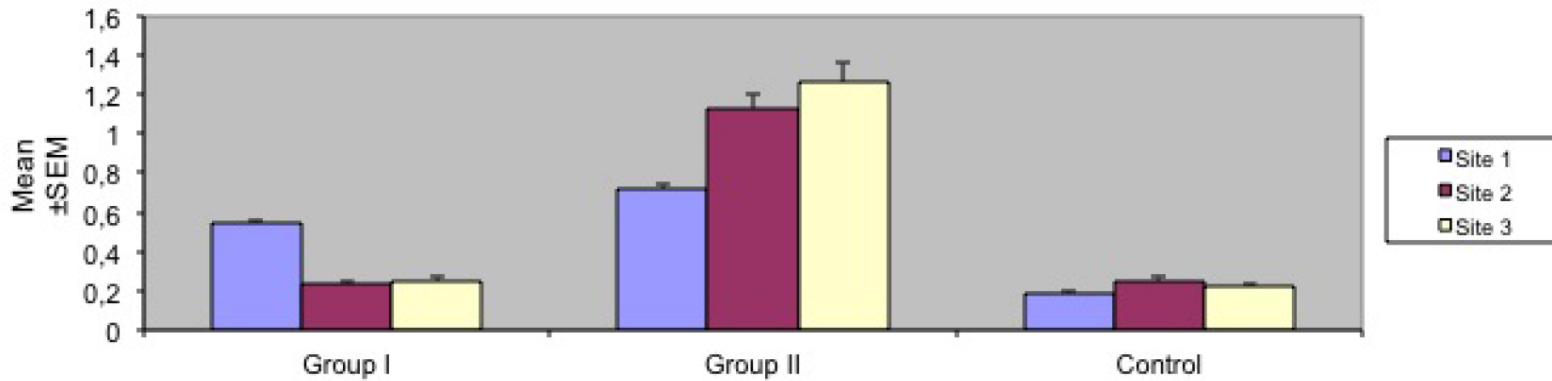**Distribution of Intergroup Measurements of Capsule Thickness at Different Sites**

Table 4 Neovascularisation values at different sites

Neovascularisation (no. of thin vessel walls per high power field)	Group I Median (Range) *	Group II Median (Range) *	Control Median (Range) *
Site 1	19 (16-22)[a, A]	28 (24-36)[b, B]	10 (8-13)[c, C]
Site 2	16 (14-20)[e, A]	33 (28-36)[d, B]	12 (9-14)[f, C]
Site 3	15 (12-19)[h, A]	29 (25-35)[g, B]	11 (9-13)[c, C]

TE and PMRT: deflation vs. inflation

- Deflation during PMRT

 -> irregular folds in the deflated expanders during radiotherapy

 -> the surrounding scar capsule contracted in response to RTx

 -> sharp edge in the expander under the breast skin

 -> result in a pressure point on the overlying breast skin

 -> the irregular fold could not be released with re-inflation after RTx

 -> expander failure

TE and PMRT: deflation vs. inflation

- To decrease the risk of irregular fold formation

 1. surgical pocket in large enough to accommodate the base of expander

 2. the expander filled to one-third to one-half of saline-filled volume

 -> subtotal deflation of the expanders for RTx

 -> no re-inflation-related complications

Conclusion

- Autologous have less complication than prosthetic reconstruction

- In prosthetic, PMRT after PI might be better than PMRT before PI

  Timing of PI after PMRT with TE: more than 6 months

  sufficient time to pass between PMRT and exchange to PI:

  successful reconstruction outcomes

- In autologous, PMRT before autologous might be better than RT

after autologous

  Timing of autologous after PMRT: more than 12 months

- In prosthetic, partially deflation with RT reduce complications