Bologna, 17 Febbraio 2017

NH Hotel De La Gare

VI ZOOM Journal Club 2016

Associazione Italiana Radioterapia Oncologica
Gruppo di Studio per la Patologia Mammaria

Radioterapia post-mastectomia

RAPPORTEUR: **LORENZA MARINO**

rem radioterapia s.r.l.

Radiotherapy post-mastectomy

- When & Why?
- After Breast Reconstruction?
- RT Technique?

A. Recht et al. Ann Surg Oncol 2016

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Nodal Status	No. of Patients	10-Year Local Recurrence Risk		20-Year Breast Cancer Mortality			20-Year Any-Cause Mortality		
		RT *v* no RT (%)	*P*	RT *v* no RT (%)	RR	*P*	RT *v* no RT (%)	RR	*P*
Mastectomy plus axillary dissection to ≥ level II (14 trials)									
Negative	700	3.0 *v* 1.6	>.1	28.8 *v* 26.6	1.18	>.1	47.6 *v* 41.6	1.23	.03
Positive	3,131	8.1 *v* 26.0	<.001	58.3 *v* 66.4	0.84	.001	65.4 *v* 70.4	0.89	.01
One to three positive	1,314	3.8 *v* 20.3	<.001	42.3 *v* 50.2	0.80	.01	53.5 *v* 56.5	0.89	>.1
One to three positive plus systemic therapy	1,133	4.3 *v* 21.0	<.001	41.5 *v* 49.4	0.78	.01	52.6 *v* 55.5	0.86	.08
≥ Four positive nodes	1,772	13.0 *v* 32.1	<.001	70.7 *v* 80.0	0.87	.04	75.1 *v* 82.7	0.89	.05
≥ Four positive nodes plus systemic therapy	1,677	13.6 *v* 31.5	<.001	70.0 *v* 78.0	0.89	.08	74.9 *v* 82.0	0.90	>.1
Mastectomy plus axillary sampling (nine trials)									
Negative	870	3.7 *v* 17.8	<.001	32.0 *v* 35.8	0.97	>.1	46.1 *v* 49.9	1.00	>.1
Positive	2,541	6.3 *v* 37.2	<.001	55.6 *v* 68.2	0.74	<.001	63.1 *v* 71.8	0.79	<.001
Mastectomy only (four trials)									
Clinically negative	2,896	16.1 *v* 35.4	<.001	50.8 *v* 53.1	0.97	>.1	62.8 *v* 61.8	1.06	>.1
Clinically positive	1,481	18.0 *v* 45.0	<.001	56.6 *v* 63.3	0.86	.03	67.1 *v* 71.5	0.91	>.1

A. Recht et al. Ann Surg Oncol 2016

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Clinical Question 1

*Is PMRT indicated in patients with **T1-2 tumors with one to three positive** axillary lymph nodes who **undergo ALND**?*

Recommendation 1a.	The panel unanimously agreed that the available evidence ***shows that PMRT reduces the risks of LRF***, any recurrence, and breast cancer mortality for patients with T1-2 breast cancer with one to three positive axillary nodes ***(type: evidence based; evidence quality: high; strength of recommendation: strong).***
Recommendation 1b.	***The decision to use PMRT should be made in a multidisciplinary fashion*** through discussion among providers from all treating disciplines early in a patient's treatment course ***(type: informal consensus; evidence quality: insufficient; strength of recommendation: strong).***
Recommendation 1c.	***Decision making must fully involve the patient***, whose values as to what constitutes sufficient benefit and how to weigh the risk of complications against this in light of the best information the treating physicians can provide regarding PMRT in her situation must be respected and incorporated into the final treatment choice ***(type: informal consensus; evidence quality: insufficient; strength of recommendation: strong).***

Clinical Question 2

*Is PMRT indicated in patients with **T1-2 tumors and a positive SNB** who do **not undergo completion ALND**?*

Recommendation	In such cases where clinicians and patients elect to omit axillary dissection, **the panel recommends that these patients receive PMRT only if there is already sufficient information to justify its use** without needing to know that additional axillary nodes are involved

Clinical Question 3

*Is PMRT indicated in patients with clinical **stage I or II cancers who have received NAST**?*

Updated Recommendation	**Patients with axillary nodal involvement that persists after should receive PMRT.** Observational data suggest a low risk of locoregional recurrence for patients who have cN0 nodes and receive NAST or who have a PCR in the lymph nodes with NAST. However, there is currently insufficient evidence to recommend whether PMRT should be administered or can be routinely omitted in these groups.

A. Recht et al. Ann Surg Oncol 2016

Clinical Question 4

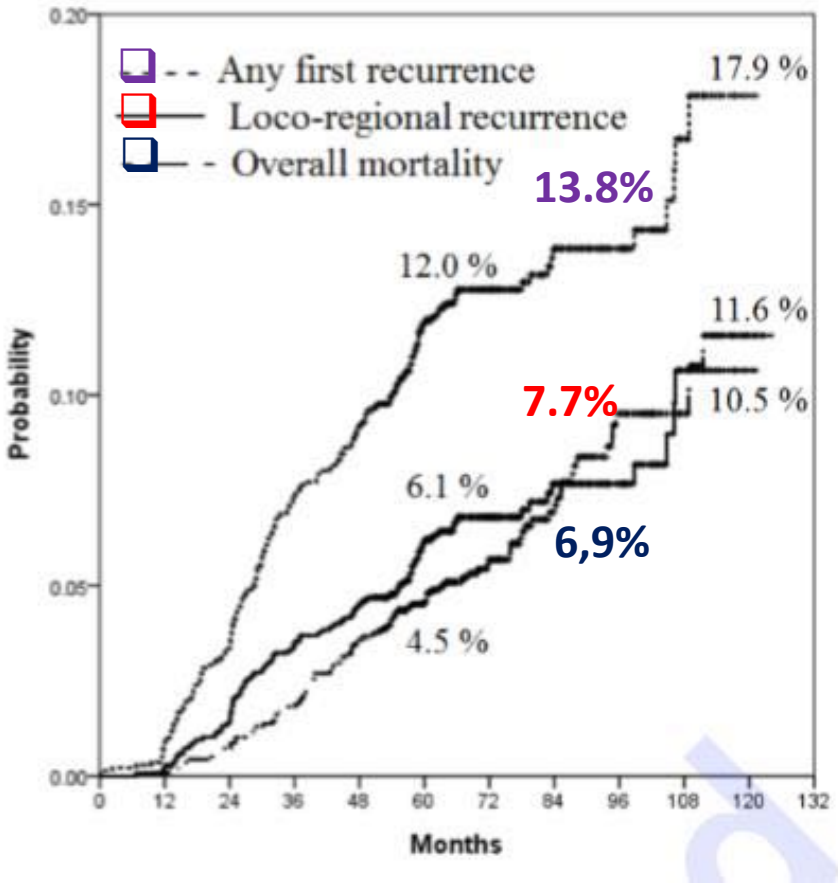
*Should RNI include both the **IMNs and supraclavicular-axillary apical nodes** when PMRT is used in patients with **T1-2 tumors with one to three positive axillary nodes**?*

Updated Recommendation	The panel recommends treatment generally be administered to **both the IMNs and the supraclavicular-axillary apical nodes** in addition to the chest wall or reconstructed breast when PMRT is used for patients **with positive axillary lymph nodes**. There may be subgroups that will experience limited, if any, benefits from treating both these nodal areas compared with treating only one or perhaps treating only the chest wall or reconstructed breast. In general, the f**ull axilla is not irradiated in those who have had ALND**, because recurrence in the dissected axilla is rare, and its inclusion may further increase toxicities, particularly lymphedema. However, there are circumstances where full axillary irradiation may be considered, such as **when ALND is not performed or after ALND in cases with extensive bulky involvement**. There are insufficient data to propose recommendations in this area at present.

A. Recht et al. Ann Surg Oncol 2016

Cancer Res Treat. 2016 Oct 19. doi: 10.4143/crt.2016.405. [Epub ahead of print]

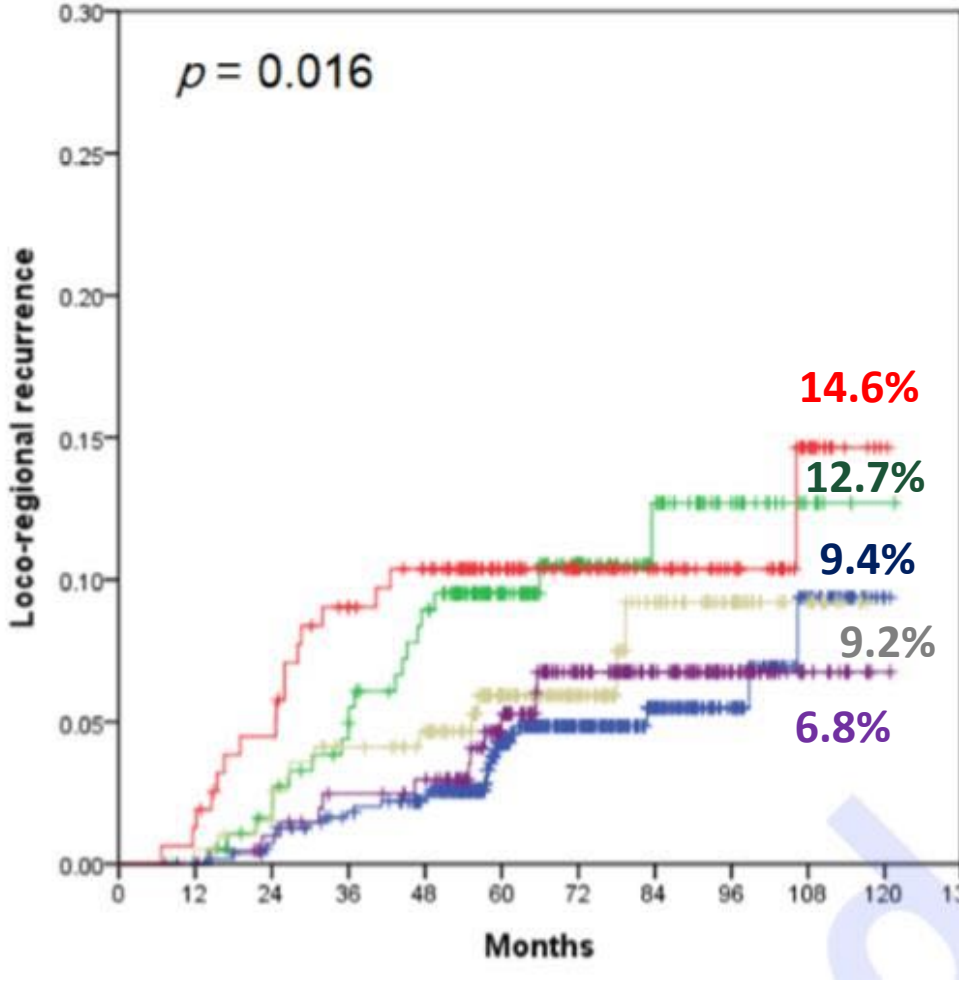
Incorporating Risk Factors to Identify the Indication of Post-Mastectomy Radiotherapy in N1 Breast Cancer Treated With Optimal Systemic Therapy: A Multicenter Analysis in Korea (KROG 14-23).

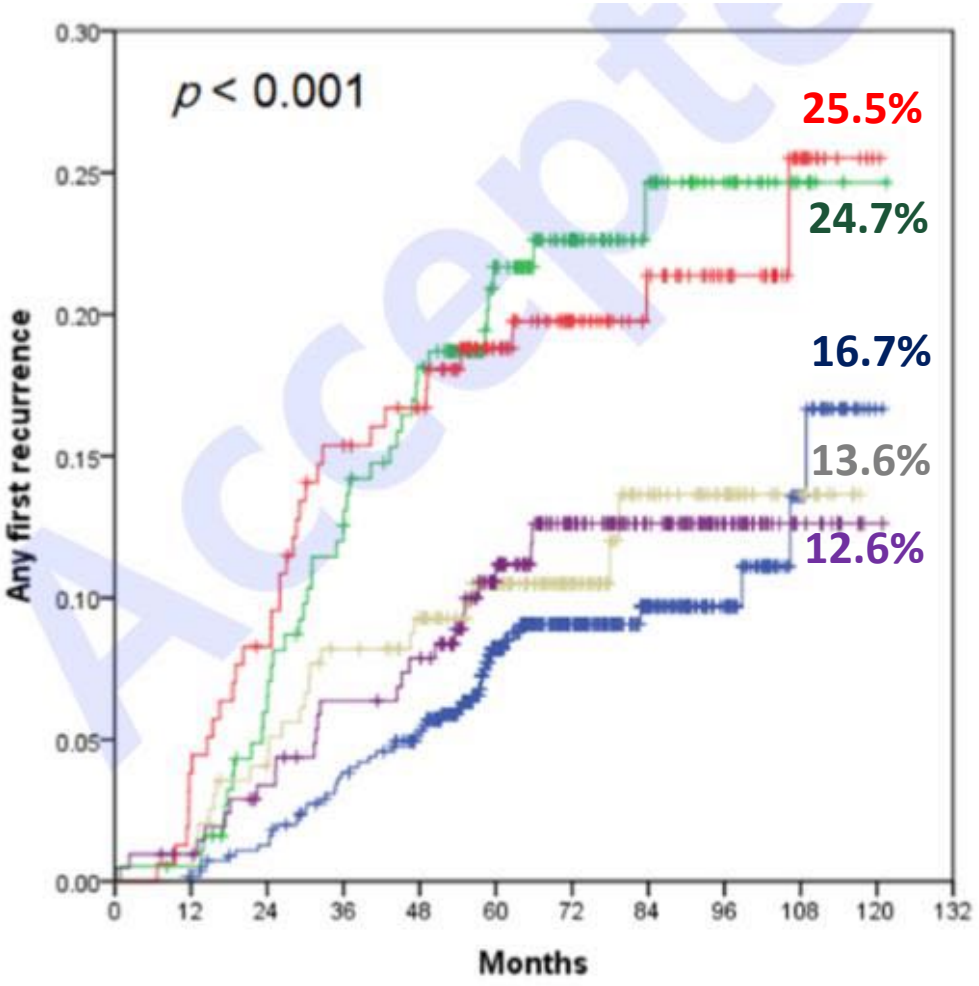


% 3N+

n

Site of recurrence	n	%
Local	39	2.8
Regional	70	5.1
Axilla	54	3.9
Internal mammary	36	2.6
Supraclavicular	47	3.4
Loco-regional	91	6.6
Distant	138	10.0



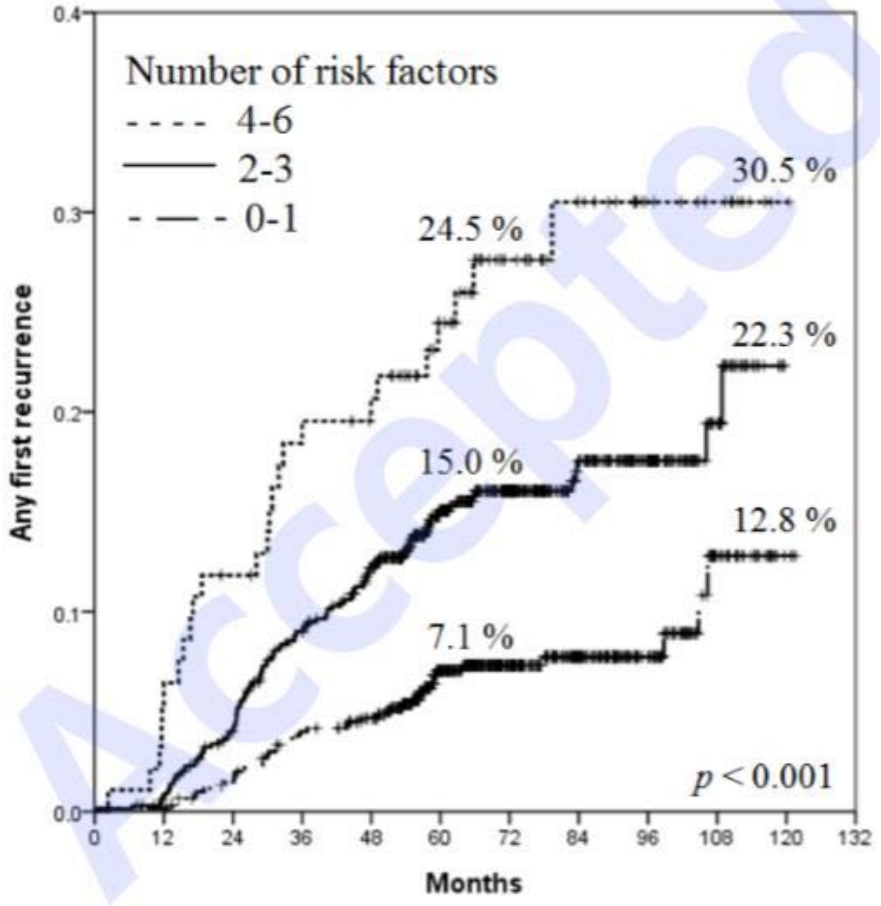


Luminal A
Luminal B
HER2
Luminal HER2
Triple negative

TN and luminal B subtypes predicted more LRR and AFR than the luminal A subtype *(all, p<0.001)*

Patients with pT1-2N1M0 breast cancer who underwent mastectomy and optimal systemic therapy showed excellent loco-regional control and disease control. The patients with **four or more risk factors may benefit from PMRT**, and those **with two or three risk factors merit consideration of PMRT.**

RISK factors
Age (≤35 years *vs* >35 years)
Tumor size (T1 *vs* T2)
margin status (negative *vs* close)
metastatic LNs (1 *vs* 2–3)
tumor grade (low-intermediate *vs* high)
biological subtype (TN *vs* others)



+ PMRT

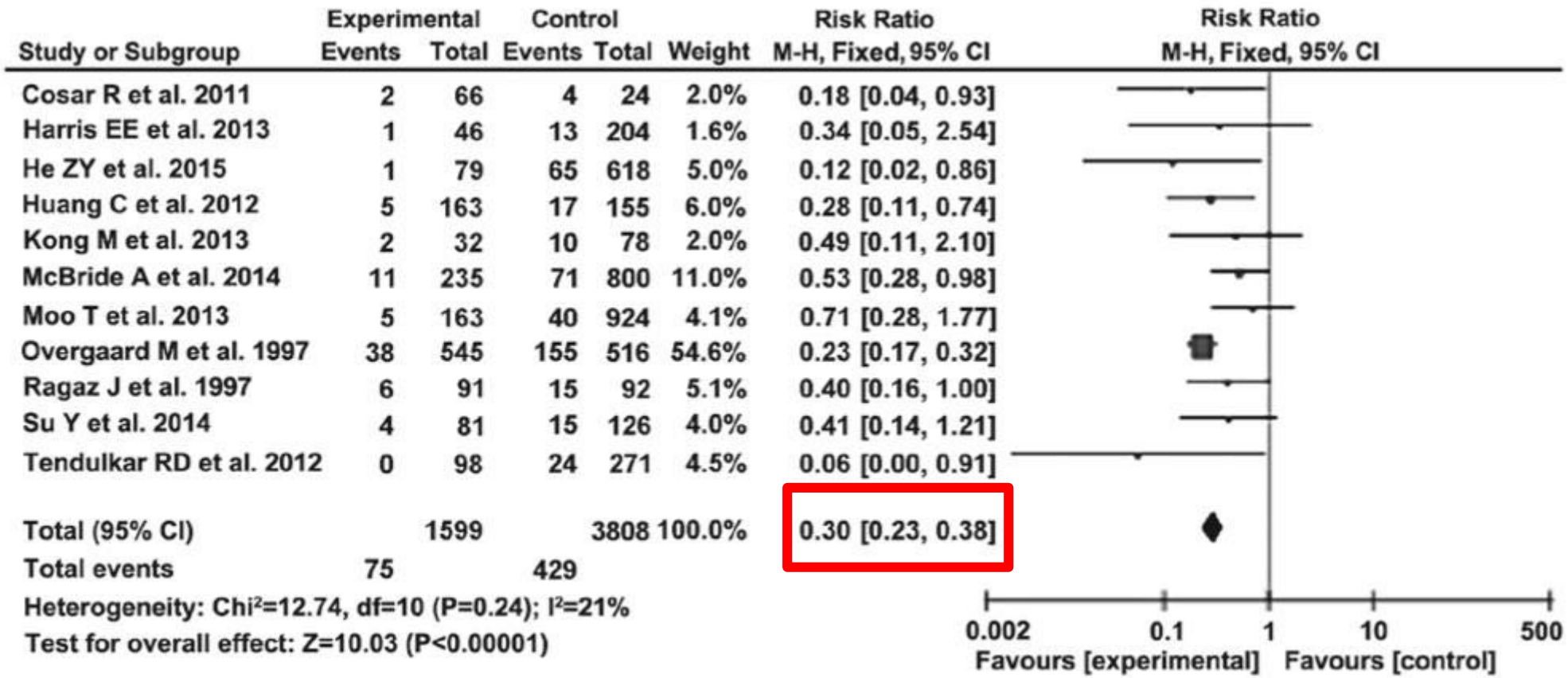
22.8%

16.7%

9.6%

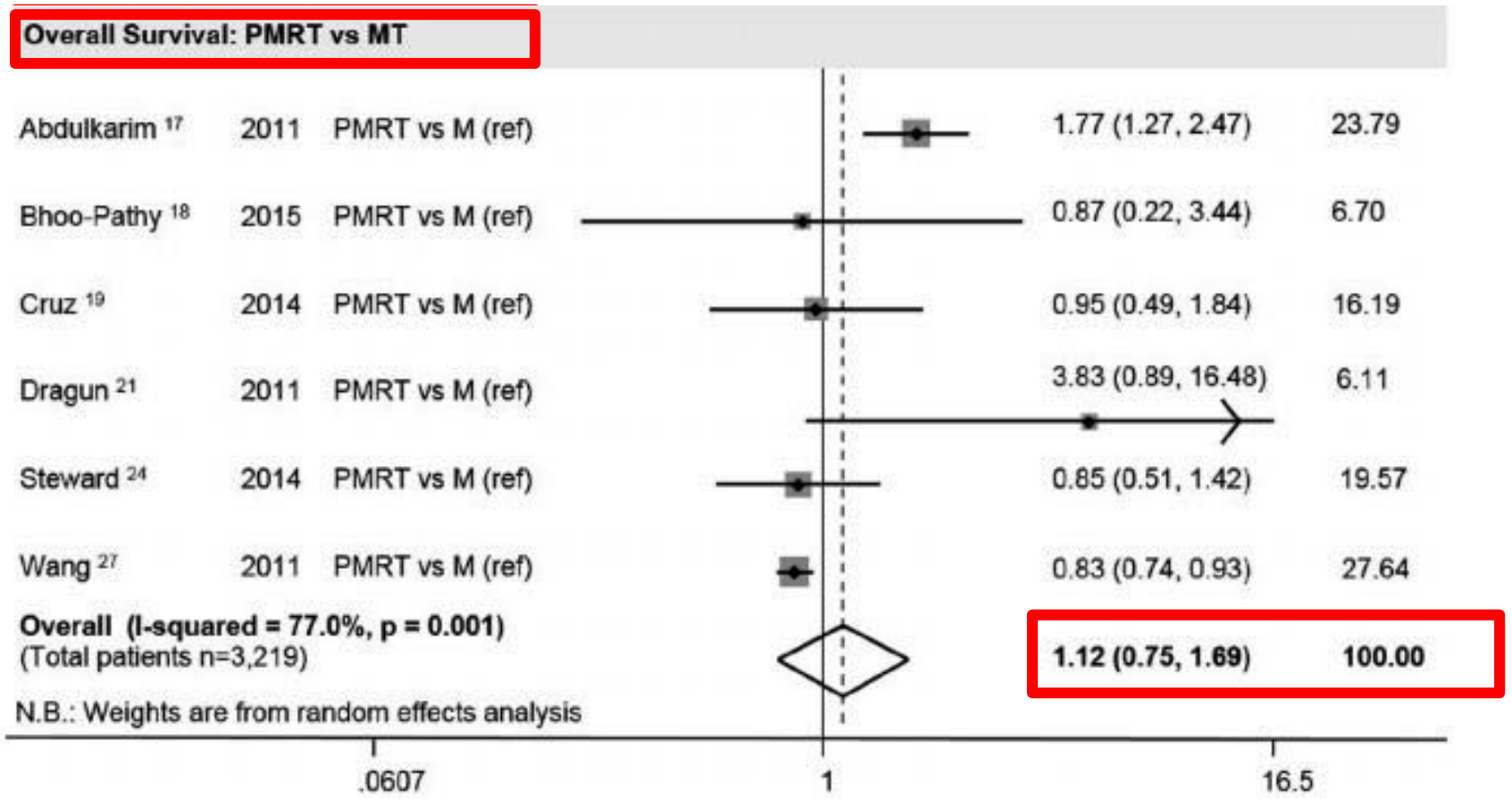
PMRT in women with breast cancer with 1-3 positive lymph nodes results is associated with a significant decrease in LRR and a relatively small OS benefit. In view of the fact that the OS benefit is relatively small at 3%, it would be reasonable to recommend PMRT to a selected group of patients with other risk factors, such as young age, estrogen receptor-negative, HER2-positive, large, poorly differentiated tumours……

LRR



Cancer Treatment Reviews 47 (2016) 12–21

Conclusions: Adjuvant radiotherapy was associated with a significantly lower risk of locoregional recurrence in TNBC patients, irrespective of the type of surgery. While radiotherapy was not consistently associated with an overall survival gain, benefits may be obtained in women with late-stage disease and younger patients.



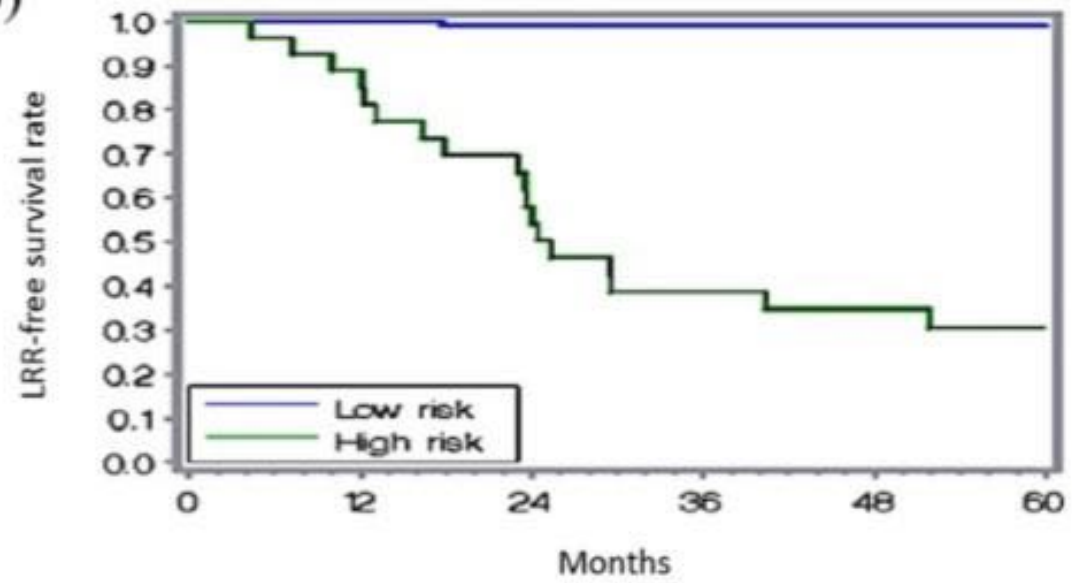
EBioMedicine 5 (2016) 74–81

Research Paper

An Eighteen-Gene Classifier Predicts Locoregional Recurrence in Post-Mastectomy Breast Cancer Patients

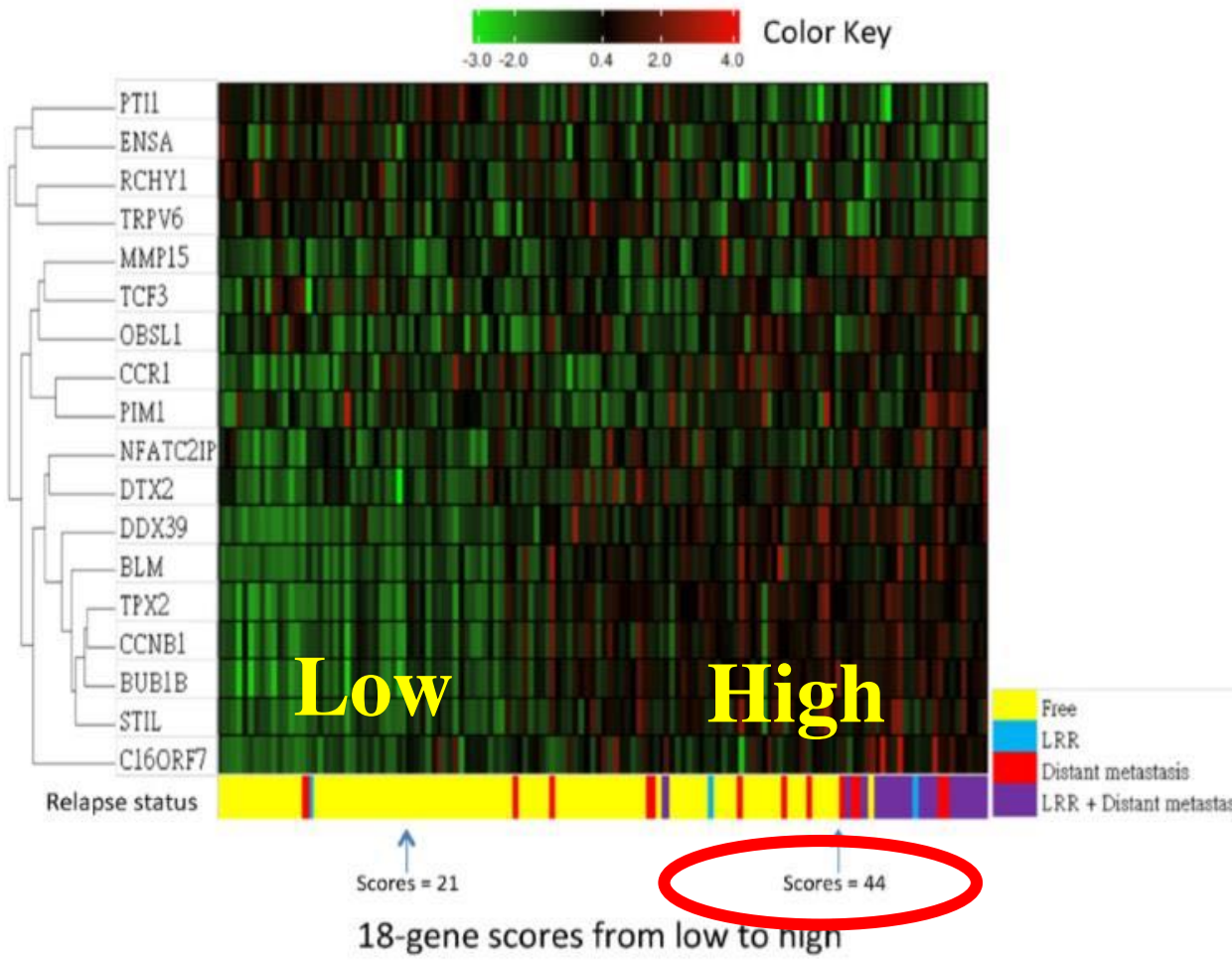
Skye H. Cheng [a,*], Chen-Fang Horng [a], Tzu-Ting Huang [a], Erich S. Huang [b], Mei-Hua Tsou [a], Li-Sur
Ben-Long Yu [d], Chii-Ming Chen [a], Andrew T. Huang [a,e]

b)



Low	# at risk	108	105	101	93	83	56
High	# at risk	27	23	15	10	8	5

Subgroup	Patient #	LRR #	5-year control rate	P value
Low risk	108	3	99%	<0.0001
High risk	27	20	30.4%	



EBioMedicine 5 (2016) 74–81

An Eighteen-Gene Classifier Predicts Locoregional Recurrence in Post-Mastectomy Breast Cancer Patients

18-gene score	Patient #	Five-year LRR-free survival rate	Five-year metastasis-free survival rate	Five-year overall survival rate
N0 patients				
Low risk	83	100.0%	95.1%	95.6%
High risk	9	50.8%	22.2%	44.4%
P value		<0.0001	<0.0001	<0.0001
N1 patients				
Low risk	24	95.2%	76.6%	77.6%
High risk	11	27.3%	22.7%	26.7%
P value		<0.0001	0.0014	0.0272
≥N2 patients	8	Too small to be analyzed		
Luminal-like subtype				
Low risk	55	100%	90.4%	90%
High risk	12	50%	31.3%	57.1%
P value		<0.0001	<0.0001	<0.0001
HER2 subtype				
Low risk	38	97.4%	94.7%	97.4%
High risk	8	0%	0%	14.6%
P value		<0.0001	<0.0001	<0.0001
Triple negative subtype				
Low risk	13	100%	92.3%	84.6%
High risk	7	14.3%	14.3%	14.3%
P value		<0.0001	0.0007	0.0050

It is essential to identify «high risk» patients for prevention of LRR and distant metastasis. The present study reveals that N0 and N1 patients can be sorted into more homogeneus subgroups by the 18-gene classifier.

The 18-panel is potentially useful in identification of the truly «high risk» patients who woud benefit most from PMRT/regional nodal irradiation, and it would omit radiotherapy in the low risk patients.

Radiotherapy post-mastectomy

- When & Why?
- After Breast Reconstrucion?
- RT Technique?

Systematic Review

Prosthetic breast reconstruction: indications and update

Tam T. Quinn[1,2], George S. Miller[1,2], Marie Rostek[1,2], Miguel S. Cabalag[1,2], Warren M. Rozen[1,2,3], David J. Hunter-Smith[1,2]

Gland Surg 2016;5(2):174-186

- **Immediate Breast Reconstruction (IBR)** : definitive reconstruction with an implant can be done either at the time of the mastectomy
  - psychological and physical benefits
  - shorter procedure time, hospital stay and recovery
  - patients with ***small, minimally ptotic breasts*** are ideal candidates for single-stage reconstruction

- **Delayed Breast Reconstruction (DBR):** two stage reconstruction with a tissue expander followed by a permanent implant and most of the time with intervening adjuvant therapy
  - tissue expansion is simple, safe and allows for preservation of the skin envelope and allows for better matched color, texture and hair-bearing qualities of the skin
  - It also allows for implantation of synthetic materials underneath the expanded tissue as the skin flaps are vascularized
  - Tissue expansion is recommended ***in patients who require adjuvant radiotherapy*** as radiotherapy can adversely affect the aesthetic outcome, and tissue expanders can impede effective and safe radiation delivery to the internal mammary and axillary lymph nodes

Radiotherapy and prosthetic breast reconstruction

Gland Surg 2016;5(2):174-186

- Capsul contracture (**RT**: 29-68% *vs* **no RT**: 10-40%)
- **Complications in RT**: 0-64% in IBR and 22-55% in DRR *vs* **NO RT**: 0-12% in IBR and 13-34% in DRR
- Higher rates of reconstruction failure (22.7%-37%)
- More likely to need revision surgery
- Lower patient satisfaction with physical and psychosocial outcome

Immediate expander/implant breast reconstruction followed by post-mastectomy radiotherapy for breast cancer: Aesthetic, surgical, satisfaction and quality of life outcomes in women with high-risk breast cancer

Meagan E. Brennan [a, b, *], Kathy Flitcroft [a, b], Sanjay Warrier [c], Kylie Snook [a, b], Andrew J. Spillane [a, b, d]

Surgical complications[d]
- No significant complications — 72.3%
- Wound infection requiring intravenous antibiotics (stage 2) — 10.6 %
- Skin flap necrosis requiring operative debridement
- Seroma requiring ≥ 3 aspirations — 4.1%
- Infection requiring removal of tissue expander
- Infection requiring removal of permanent prosthesis
- Leaking tissue expander requiring early exchange
- Wound dehiscence requiring operative repair (LD donor site)

Contralateral procedures
Wide local excision
Mastectomy, bilateral implant reconstruction
Mastectomy, bilateral free flap reconstruction
Reduction/mammaplasty/mastopexy

Tumor and treatment characteristics	N	%
Histological type		
– Invasive ductal carcinoma	33	67.3
– Invasive lobular carcinoma	12	24.5
– Mixed	2	4.1
– Other	2	4.1
Histological grade		
– Grade 1	1	2.0
– Grade 2	22	44.9
– Grade 3	25	51.0
– Unknown	1	2.0
Tumor size (mm); largest invasive focus at surgery[a]		
– Mean	51.0	–
– Median	40.0	–
– Range	0–160	–
Estrogen receptor		
– Positive	40	81.6
– Negative	9	18.4
Progesterone receptor		
– Positive	39	79.6
– Negative	10	20.4
HER2 receptor		
– Positive	12	24.5
– Negative	37	75.5
Lymph node status		
– Node negative	12	25.5
– Node positive	37	74.5
– Mean (median) number of positive nodes	3.6 (2.0)	
Radiotherapy regions treated		
– Chest wall	47	100
– Supraclavicular fossa[b]	29	61.7
– Internal mammary chain[b]	8	17
– Axilla[b]	3	6.4
Time surgery to start chemotherapy (days)		
Range	14 to 66	–
Median (mean)	30.0 (32.2)	–
Interquartile mean	31.1	–
Chemotherapy		
Yes	42	89.4
Neo-adjuvant	5	10.6
Adjuvant	37	77.6
– No	5	10.6

Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy

S. Al-Himdani [a], S. Timbrell [a], K.T. Tan [a], J. Morris [b], N.J. Bundred [a,*]

S. Al-Himdani et al./EJSO 42 (2016) 935e941

	Simple (n = 462)	SSM (n = 115)	Comparison of groups
Age (years)	61.6 (22–96)	49.1 (29–69)	$p < 0.001$[a]
Symptomatic	314 (68%)	65 (56%)	$p = 0.028$[b]
Grade			
0	11 (2%)	2 (2%)	$p = 0.12$[c]
1	30 (6%)	7 (6%)	
2	176 (38%)	60 (52%)	
3	245 (53%)	46 (40%)	
Tumour size (n = 548)			
<15 mm	98 (22%)	28 (26%)	$p = 0.02$[c]
15–25 mm	141 (32%)	48 (44%)	
>25 mm	201 (45%)	32 (30%)	
No. positive lymph nodes (n = 536)			
0	240 (55%)	79 (78%)	$p < 0.001$[c]
1–4	119 (27%)	18 (18%)	
>4	76 (17%)	4 (4%)	
Tumour types			
IDC	323 (70%)	61 (53%)	$p = 0.001$[b]
IDC and DCIS	181 (39%)	49 (43%)	$p = 0.57$[b]
DCIS (pure)	62 (14%)	41 (36%)	$p < 0.001$[b]
ILC	79 (17%)	8 (7%)	$p = 0.008$[b]
Margin status (n = 565)	68 (15%)	33 (29%)	$p = 0.001$[b]
Incomplete (≤1 mm)			

***RT** 28% in simple vs 11% in SSM*

Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy

Characteristic	Overall (n = 577)	Simple (n = 466)	SSM (n = 115)
Mastectomy group			
SSM (vs simple)	1.14 (0.53, 2.42)		
	p = 0.74		
Age (years)	0.99 (0.97, 1.02)	1.0 (0.97, 1.03)	0.92 (0.84, 0.99)
	p = 0.56	p = 0.80	p = 0.033
Symptomatic	1.31 (0.64, 2.66)	1.84 (0.74, 4.56)	0.63 (0.17, 2.35)
(vs screened)	p = 0.46	p = 0.19	p = 0.49
Grade 3	2.61 (1.28, 5.30)	2.44 (1.06, 5.57)	2.98 (0.74, 11.9)
	p = 0.006	p = 0.035	p = 0.12
ER positive (n = 531)	0.77 (0.34, 1.77)	0.75 (0.30, 1.86)	0.98 (0.12, 8.13)
	p = 0.54	p = 0.54	p = 0.98
PR positive (n = 525)	0.70 (0.34, 1.44)	0.61 (0.28, 1.33)	1.72 (0.21, 14.3)
	p = 0.34	p = 0.21	p = 0.62
HER 2 status (n = 158)	0.37 (0.09, 1.63)	0.26 (0.03, 2.02)	0.60 (0.07, 5.43)
[3 vs 0,1,2]	p = 0.19	p = 0.20	p = 0.65
Tumour size (n = 548)			
<15 mm	1	1	1
15–25 mm	1.41 (0.53, 3.75)	0.86 (0.29, 2.56)	1
>25 mm	1.68 (0.66, 4.27)	1.26 (0.48, 3.28)	1.28 (0.30, 5.34)
	p = 0.54	p = 0.69	p = 0.74[a]
Staging			
Stage 0/1	1	1	1
Stage 2	2.12 (0.94, 4.80)	4.64 (1.33, 16.1)	0.71 (0.14, 3.51)
Stage 3	3.79 (1.57, 9.15)	7.26 (2.00, 26.4)	3.23 (0.39, 26.9)
	p = 0.013	p = 0.011	p = 0.45
Lymphovascular invasion	2.66 (1.35, 5.25)	3.26 (1.52, 6.96)	1.02 (0.13, 8.12)
	p = 0.005	p = 0.002	p = 0.99
Positive lymph nodes			
0	1	1	1
1–4	4.37 (1.83, 10.4)	9.41 (2.68, 33)	0.89 (0.10, 7.63)
>4	7.49 (3.01, 18.7)	14.5 (3.98, 53)	3.69 (0.43, 31.6)
	p < 0.001	p < 0.001	p = 0.47[b]
Any DCIS (pure or with IDC (n = 571)	0.84 (0.43, 1.61)	0.57 (0.26, 1.23)	
	p = 0.60	p = 0.15	
Margin status			
Complete	1	1	1
Incomplete (≤1 mm)	2.92 (1.48, 5.76)	2.86 (1.25, 6.56)	3.34 (0.90, 12.4)

Prediction of margin involvement and local recurrence after skin-sparing and simple mastectomy

S. Al-Himdani [a], S. Timbrell [a], K.T. Tan [a], J. Morris [b], N.J. Bundred [a,*]

Characteristic	Overall hazard ratio
Overall	
Mastectomy type[a]	
Simple	1
SSM	1.05 (0.43, 2.56)
	p = 0.91
Positive lymph nodes	
0	1
1–4	4.64 (1.93, 11.2)
>4	7.97 (3.16, 20.1)
	p < 0.001
Margin status	
Complete	1
Incomplete (≤1 mm)	3.28 (1.57, 6.86)
	p = 0.002
Lymph node negative patients	
Mastectomy type	
Simple	1
SSM	4.8 (1.1, 19.9)
	p = 0.033

In patients with involved margins, the risk of local recurrence is increased and oncological safety compromised if no further surgery is performed. Oncological safety should be prioritised above the aesthetic appearance in these patients. We now ensure clear margins by re-excision of the margins after SSM if necessary, despite potential embarrassment to the Surgeon at explaining the issues to the patient.

Careful patient counselling before surgery also needs to address these issues to give full information on the risks of oncological relapse and to consider whether breast conserving surgery is possible, rather than mastectomy for an individual patient.

Radiotherapy post-mastectomy

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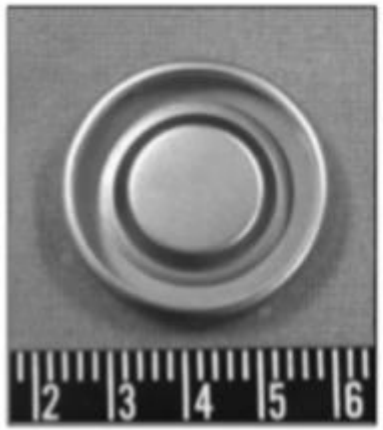
- RT Technique?

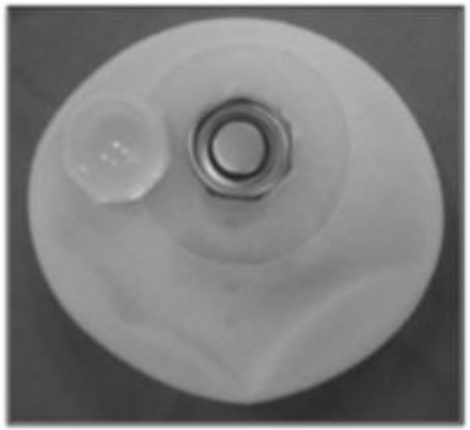
Journal of Medical Imaging and Radiation Oncology **60** (2016) 138–145

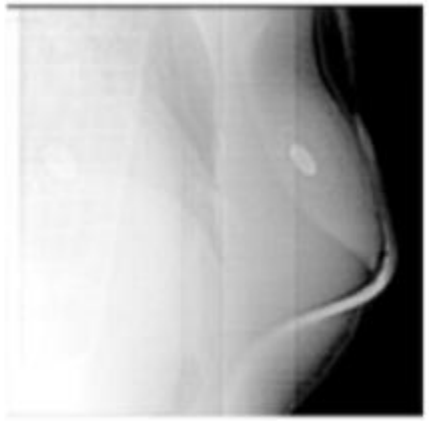
RADIATION ONCOLOGY—ORIGINAL ARTICLE

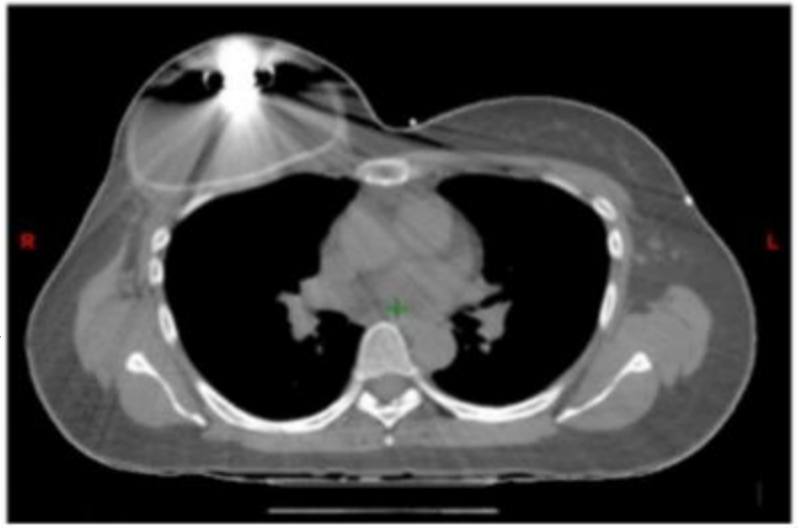
In vivo dosimetric impact of breast tissue expanders on post-mastectomy radiotherapy

Harriet E Gee,[1,2]* Fiona Bignell,[3]* David Odgers,[1] Simran Gill,[1] Darren Martin,[1] Joanne Toohey[1] and Susan Carroll[1]









- Underdosage of the PTV in the range of 10% (***Med Phys 2005; 32: 1640–6***)
- Monte Carlo simulation predicted reduction of absorbed dose to be **7–13% for 6 MV** and **6% for 18 MV** beams (***IJROBP 2006; J Appl Clin Med Phys 2011***)
- A recent simulation using Eclipse planning software (Varian Medical Systems, Palo Alto, CA, USA) predicted no significant change in dose (***PLoS ONE 2013***)

Journal of Medical Imaging and Radiation Oncology 60 (2016) 138–145

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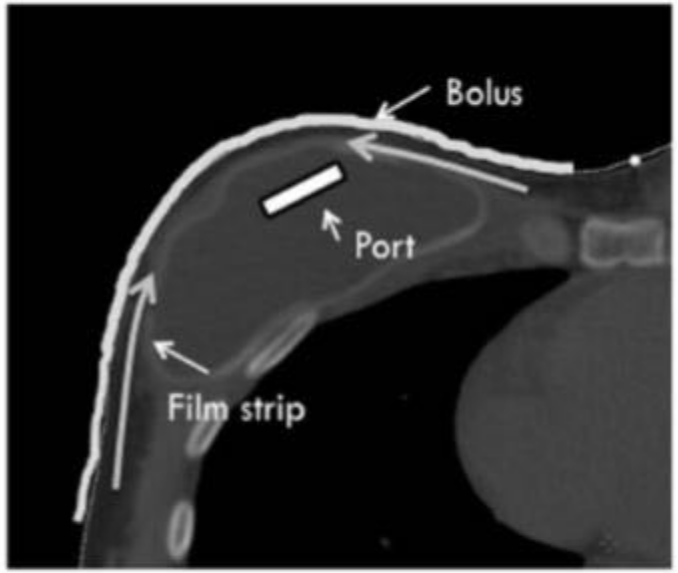
Harriet E Gee,[1,2]* Fiona Bignell,[3]* David Odgers,[1] Simran Gill,[1] Darren Martin,[1] Joanne Toohey[1] and Susan Carroll[1]

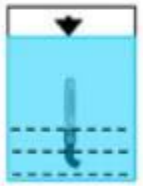
16 pz



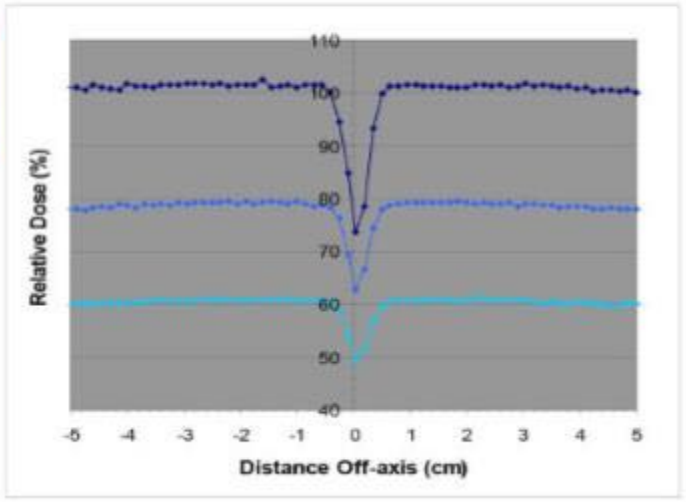
Ex vivo dosimetry

- **The average reduction in dose in the lateral 'cold-spot'** :7.5% (range 3.6–11.5%)
- **The average reduction in dose in the medial 'cold-spot'**:6.5% (range 4.5–8.7%)
- The average surface area of the 'cold-spots' was 1.07 cm^2 (range 0.39–2.36)

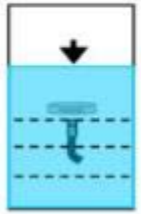
(a)



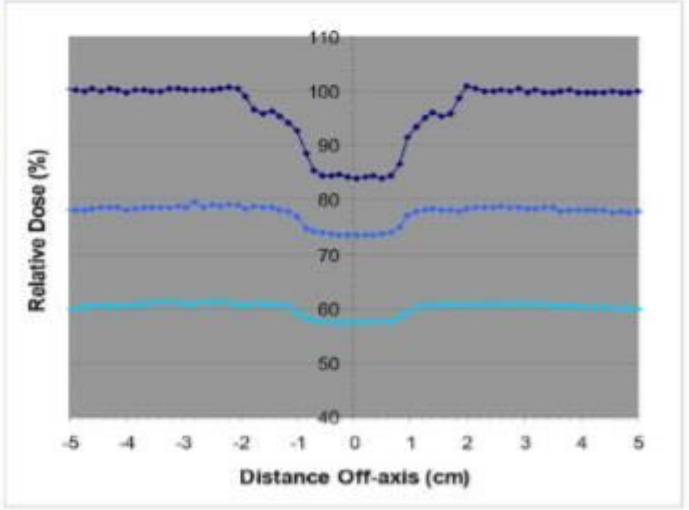
28%



(b)

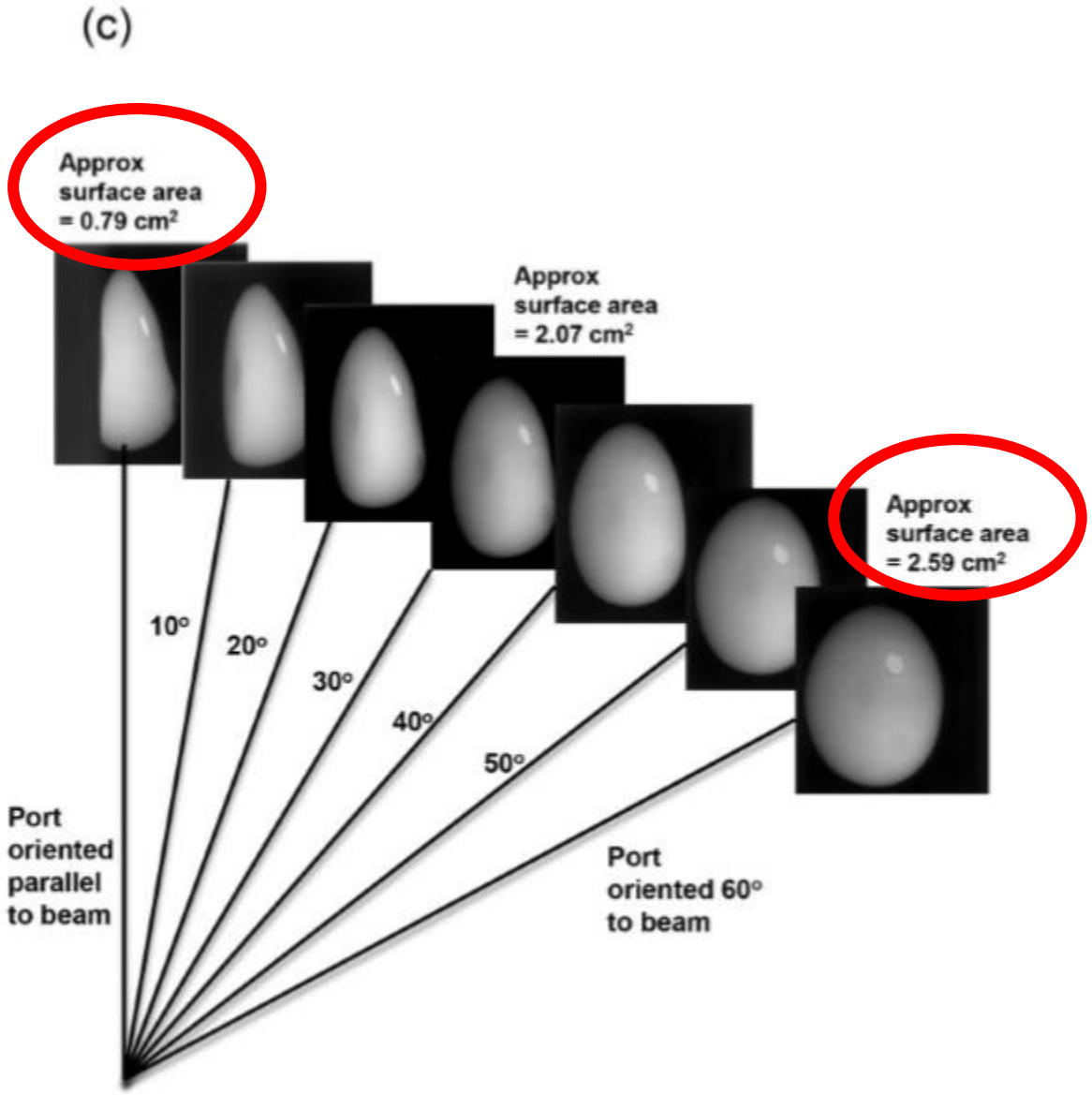


16%



Ex vivo dosimetry

Dose is attenuated in the ‘shadow’ of the tissue expander port in patients receiving PMRT. This is likely to be clinically insignificant for most, but centres should undertake appropriate measurements before utilising TPS predictions.



In conclusion, PMRT without usage of a bolus resulted in a low rate of severe acute dermatitis without an apparent increase in local recurrence.
PMRT without usage of a bolus may be reasonable, especially for patients with a luminal subtype.

Factor		Number
Age		Median 53 years (30–79)
Histology	Ductal carcinoma	109 (89%)
	Lobular carcinoma	9 (7%)
	Other	4 (3%)
Subtype	Luminal A	44 (36%)
	Luminal B	30 (25%)
	HER-2-enriched	15 (12%)
	Triple-negative	31 (25%)
	Unknown	2 (2%)
With T4 components (clinical and/or pathological)	No	66 (54%)
	Yes	56 (46%)
Number of pathologically metastatic lymph nodes	0	23 (19%)
	1–3	29 (24%)
	4–9	44 (36%)
	10 or more	26 (21%)
Lymphatic invasion status	0–1	86 (70%)
	2–3	33 (27%)
	Unknown	3 (2%)

Subtype	Number of patients	Incidence of local recurrence
Luminal A	44	0 (0%)
Luminal B	30	2 (6.7%)
Her-2-enriched	15	2 (13%)
Triple-negative	31	8 (26%)
Unknown	2	0 (0%)

- ✓ **Grade 2 dermatitis** : 11 pz (9.0%)
- ✓ No Grade 3–4 dermatitis
- ✓ Other Grade 2 adverse effects: 4 pz (arm edema: 2, nausea: 1, pneumonitis: 1)

Journal of Radiation Research, Vol. 00, No. 00, 2016, pp. 1–5

Eravamo insieme,
tutto il resto
l'ho scordato.....

GRAZIE