Fattori prognostici e sottotipi molecolari: interazioni con la RT

B. Meduri

II Zoom Journal Club 2012

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

RADIATION ONCOLOGY

RESEARCH Open Access

Association of single nucleotide polymorphisms in the genes *ATM*, *GSTP1*, *SOD2*, *TGFB1*, *XPD* and *XRCC1* with risk of severe erythema after breast conserving radi[illegible]y

RESEARCH Open Access

SNPs in DNA repair or oxidat[illegible]tress genes and late subcutaneous fibrosis in p[illegible]ts following single shot partial breast irradia[illegible]

Journal of Experimental & Clinical Cancer Research

3

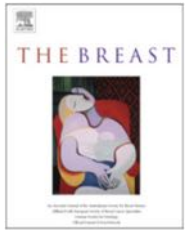
Individual patient data meta-analysis shows no association between the SNP rs1800469 in TGFB and late radiotherapy toxicity

Triple Negative Breast Cancer Is Associated With an Increased Risk of Residual Invasive Carcinoma After Lumpectomy

Low p53 Binding Protein 1 (53BP1) Expression Is Associated With Increased Local Recurrence in Breast Cancer Patients Treated With erving Surgery and Radiotherapy

Prognostic Va f Molecular Subtypes, Ki67 Expression and Impact tomy Radiation Therapy in Breast Cancer Pat Negative Lymph Nodes After Mastectomy

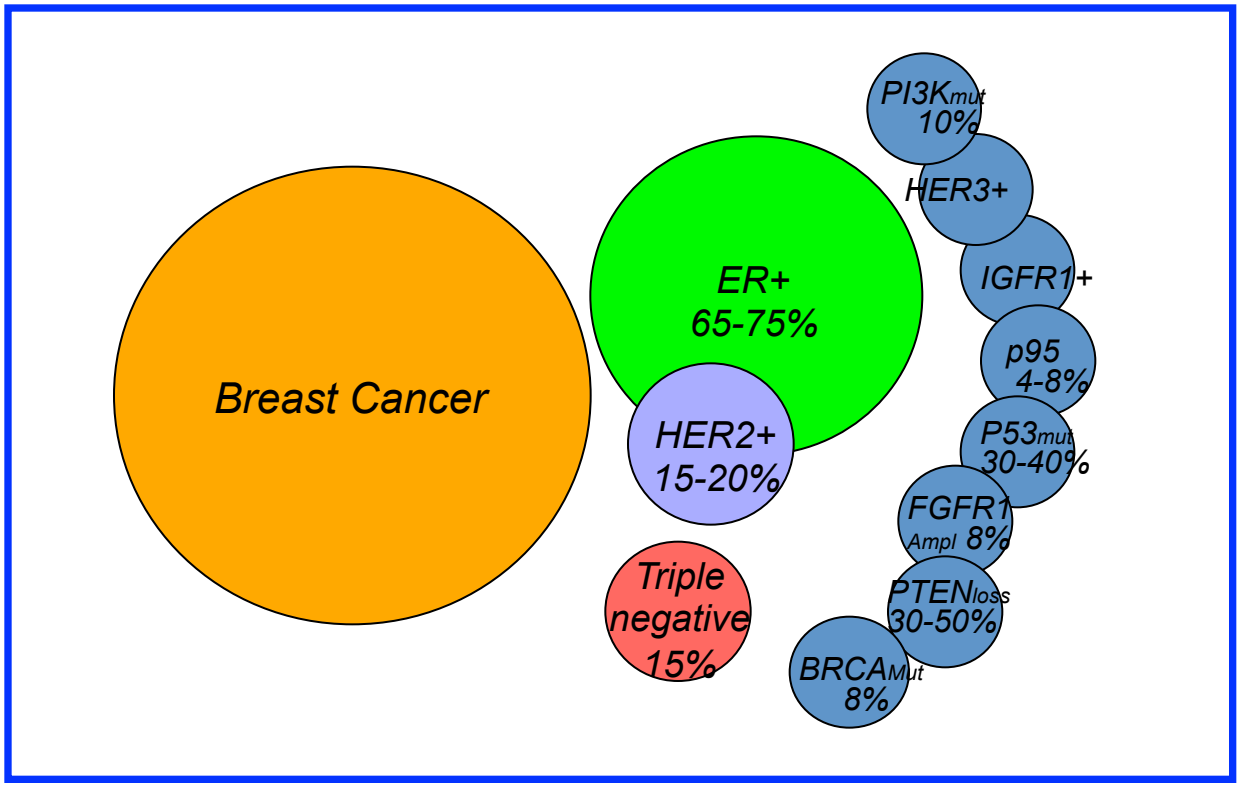
Predictive value of breast cancer molecular subtypes Chinese patients with four or more positive nodes after pos tomy radi herapy



Brain metastases from breast cancer: proposition of new prognostic score including molecular subtypes and treatment

Background

Breast Cancer(s)



Background

"Classic" prognostic factor

- Node involvement
- Tumor size
- Histologic grade
- ER and PgR expression
- HER-2 amplification
- Markers of proliferation (Ki-67 or MIB-1)

Background

Predictive factor

Local recurrence after BCT or mastectomy

- Clinical and Histopathologic Factors
- Immunohistochemical Markers
- Molecular Subtypes
- Gene Expression Profiling

RT Sensitivity

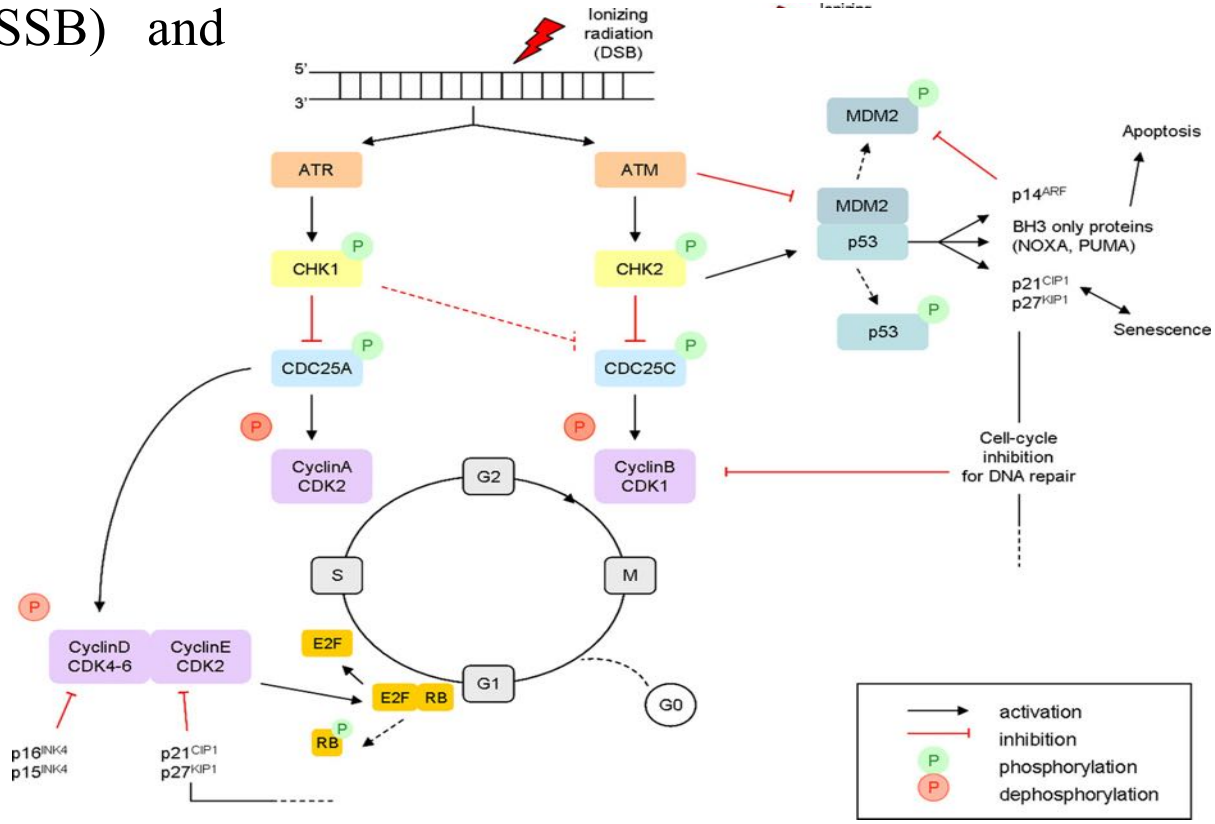
- DNA Double-Strand Break Repair
- Gene expression In Vitro Studies
- Gene expression In Vivo Studies

Background

RT-induced damage and DNA damage response

- Single-strand breaks (SSB) and double-strand breaks (DSB)

- **DNA damage response**
  - DNA repair mechanisms
  - Cell-cycle checkpoints
  - Apoptosis



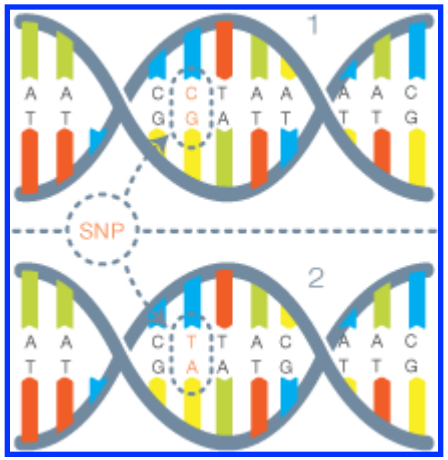
Borchiellini D et al. *Cancer Treatment Reviews* 2012, 38:737

Background

Human genome variations

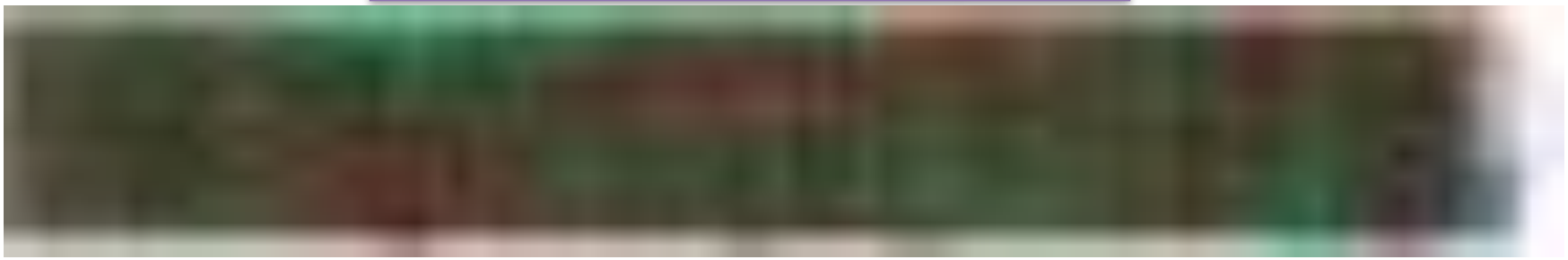
- Tandem repeats, copy number variations of a gene, single-nucleotide polymorphisms (SNPs)

- ***SNPs*** (90% of cases)
  - DNA sequence alteration affecting a single nucleotide, a point mutation
  - No major deleterious clinical consequences
  - Alter gene expression or protein function, predisposing subjects to disease or influencing their response to a given treatment



Background

Molecular subtype

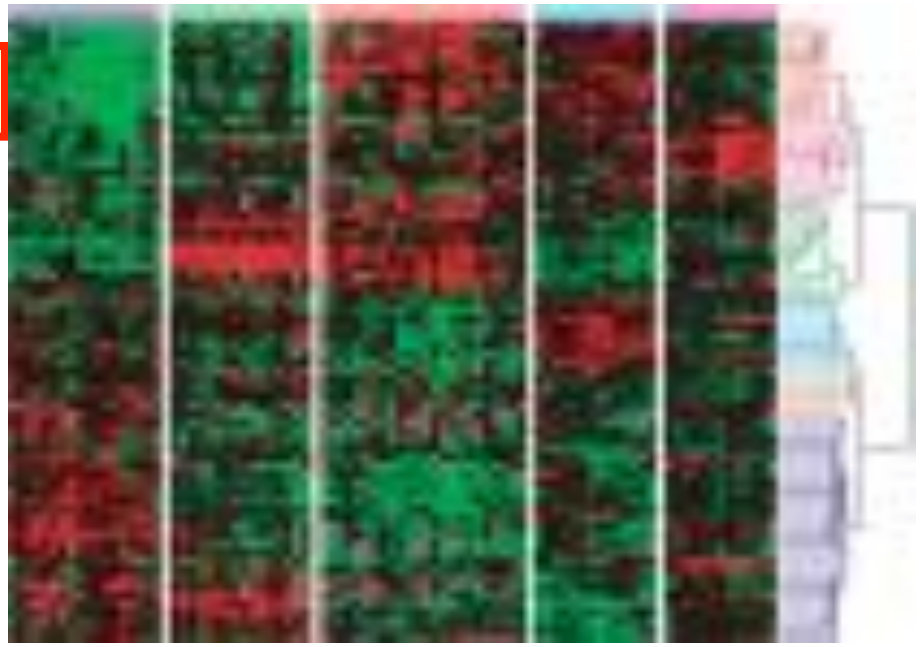


(ER - , PR - and HER2 -) **Basal-like subtype**

ERBB2+ enriched

Luminal B

Luminal A



Perou CM. *Nature* 2000; 406, 747–752
Sørlie T. *PNAS* 2001; 98 (19), 10869-74

1t

SNPs and toxicity

Acute toxicity

Association of single nucleotide polymorphisms in the genes *ATM*, *GSTP1*, *SOD2*, *TGFB1*, *XPD* and *XRCC1* with risk of severe erythema after breast conserving radiotherapy

... We investigated in a retrospective study on breast cancer patients the association of these SNPs with the risk of acute tissue toxicity in terms of erythema, with special focus on the relevance of breast size.

Raabe et al. *Radiation Oncology* 2012, 7:65

SNPs and toxicity

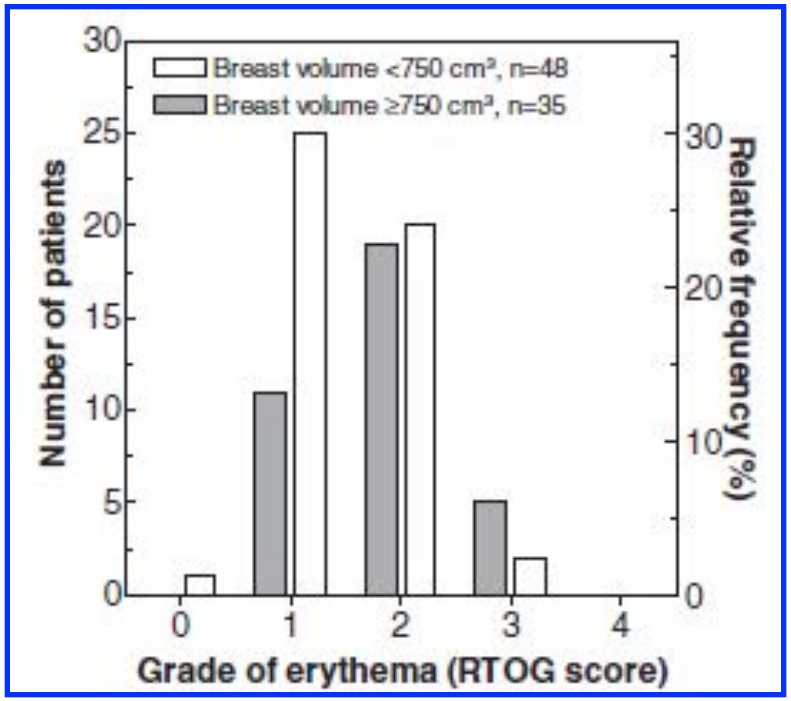
Materials and methods

- Blood samples collected from 83 pts with breast cancer Stage I/II treated with QUART
- DNA extracted from the whole blood of the patients using a genomic extraction kit
- It was tested using the two-sided exact Cochran-Armitage trend test:
  - Association between breast volume and risk of erythema
  - Associations between erythema grade and each individual SNP

Raabe et al. *Radiation Oncology* 2012, 7:65

SNPs and toxicity

Results



Significant association between the risk of *erythema* and *breast volume* (OR= 2.55, p = 0.041)

			all patients (n = 83)					
Gene (codon)	Genotype	aa	n (%)	G0/1[a]	G2/3[a]	OR[b]	95% CI[c]	P[d]
ATM	GG		63 (76)	28	35	1		
(1853)	GA		18 (22)	9	9	1.18	0.45 – 3.25	0.826
	AA		2 (2)	0	2	1.38	0.20 – 10.59	
GSTP1	AA		37 (45)	19	18	1		
(105)	AG		38 (45)	12	26	1.01	0.49 – 2.09	1.000
	GG		8 (10)	6	2	1.02	0.24 – 4.35	
TGFB1	CC		29 (35)	14	15	1		
(pos-509)	CT		40 (48)	18	22	1.26	0.65 – 2.50	0.530
	TT		14 (17)	5	9	1.59	0.42 – 6.24	
XPD [e]	GG		34 (42)	19	15	1		
(751)	GT		38 (46)	14	24	1.85	0.90 – 4.00	0.098
	TT		10 (12)	3	7	3.44	0.81 – 16.01	
XRCC1	GG		36 (43)	17	19	1		
(399)	GA		33 (40)	13	20	1.02	0.54 – 1.93	1.000
	AA		14 (17)	7	7	1.04	0.29 – 3.73	

Raabe et al. *Radiation Oncology* 2012, 7:65

SNPs and toxicity

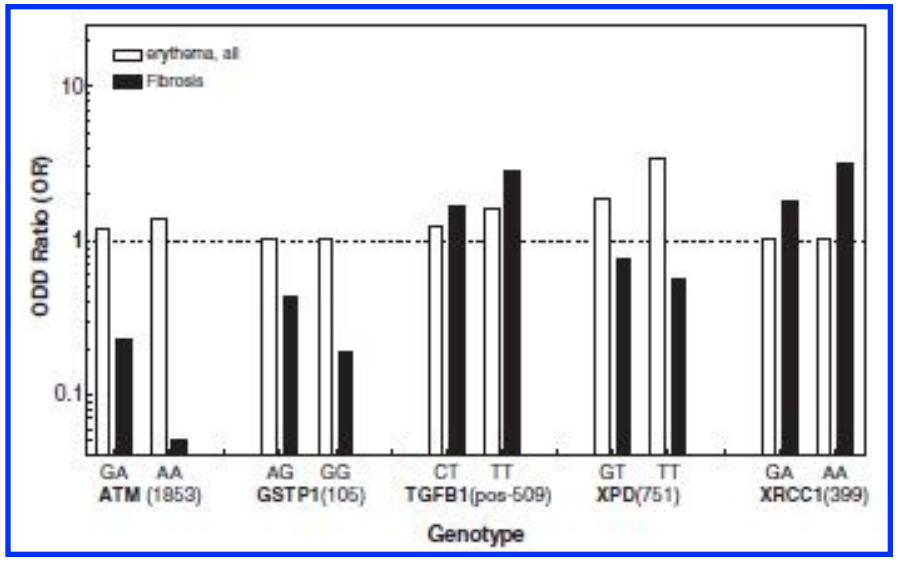
Results

		patients with breast volume <750 cm³ (n = 48)							patients with breast volume ≥750 cm³ (n = 35)					
Gene (codon)	Genotype	n (%)	G0/1[a]	G2/3[a]	OR[b]	95% CI[c]	P[d]	aa	n (%)	G0/1[a]	G2/3[a]	OR[b]	95% CI[c]	P[d]
ATM	GG	36 (75)	20	16	1				27 (77)	8	19	1	0.19 – 5.68	
(1853)	GA	11 (23)	6	5	1.43	0.38 – 5.67	0.573		7 (20)	3	4	0.92	0.04 – 32.21	1.000
	AA	1 (2)	0	1	2.05	0.15 – 32.15			1 (3)	0	1	0.84		
GSTP1	AA	21 (44)	12	9	1				16 (46)	7	9	1		
(105)	AG	21 (44)	10	11	0.98	0.39 – 2.44	1.000		17 (48)	2	15	1.25	0.32 – 5.29	0.772
	GG	6 (12)	4	2	0.96	0.15 – 5.97			2 (6)	2	0	1.56	0.10 – 28.03	
TGFB1	CC	18 (38)	13	5	**1**				11 (31)	1	10	1		
(pos-509)	CT	24 (50)	12	12	**3.10**	**1.11 –10.21**	**0.028**		16 (46)	6	10	0.36	0.10 – 1.14	0.083
	TT	6 (12)	1	5	**9.58**	**1.23 – 104.30**			8 (23)	4	4	0.13	0.01 – 1.29	
XPD [e]	GG	20 (43)	12	8	1				14 (40)	7	7	**1**		
(751)	GT	20 (43)	10	10	1.42	0.59 – 3.59	0.420		18 (51)	4	14	**3.95**	**0.91 – 22.75**	**0.046**
	TT	7 (14)	3	4	2.03	0.34 – 12.89			3 (9)	0	3	**15.62**	**0.84 – 517.40**	
XRCC1	GG	25 (52)	14	11	1				11 (31)	3	8	1		
(399)	GA	17 (35)	9	8	1.13	0.46 – 2.76	0.840		16 (46)	4	12	0.62	0.20 – 1.84	0.464
	AA	6 (12)	3	3	1.27	0.21 – 7.63			8 (23)	4	4	0.39	0.04 – 3.39	

Raabe et al. *Radiation Oncology* 2012, 7:65

SNPs and toxicity

Results



Odd ratios with respect to risk of erythema compared with the OR previously determined for risk of fibrosis

Association of the **combination of all SNPs** with erythema was tested: **no significant association** with risk of erythema for
all patients (OR = 1.20; p = 0.209)
small breast vol (OR = 1.36; p = 0.098)
large volume (OR = 0.89; p = 0.712)

Raabe et al. *Radiation Oncology* 2012, 7:65

SNPs and toxicity

Conclusion

... this study demonstrates ... that *significant associations* between a specific SNP and **risk of erythema** can be identified **if patients are grouped by their breast volume**.

The combination of SNPs using risk alleles according to erythema is substantially **different from** a risk score previously defined **for risk of fibrosis**

... these results need to be replicated in an *independent and larger study*

2t

SNPs and toxicity

Journal of Experimental & Clinical Cancer Research

Late toxicity

SNPs in DNA repair or oxidative stress genes and late subcutaneous fibrosis in patients following single shot partial breast irradiation

... to evaluate the potential association between SNPs related response to **radiotherapy injury**, such as genes related to **DNA repair** or enzymes involved in **anti-oxidative activities** in patients who underwent a *Single Shot 3D-CRT PBI* after BCS...

Falvo et al. *Journal of Experimental & Clinical Cancer Research* 2012, 31:7

SNPs and toxicity

Materials and methods

- 57 patients underwent BCS and a sentinel node biopsy and/or axillary dissection for early breast adenocarcinoma
- Single dose **3D-CRT APBI** (18 Gy or 21 Gy)
- **Fibrosis** assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (*CTCAE* 3.0).
- **SNPs**: XRCC3 C18067T (Thr241Met), XRCC3 A4541G (5'-UTR), XRCC1 G28152A (Arg399Gln), GSTP1 A313G (Ile105-Val) and RAD51 G135C (untranslated region).

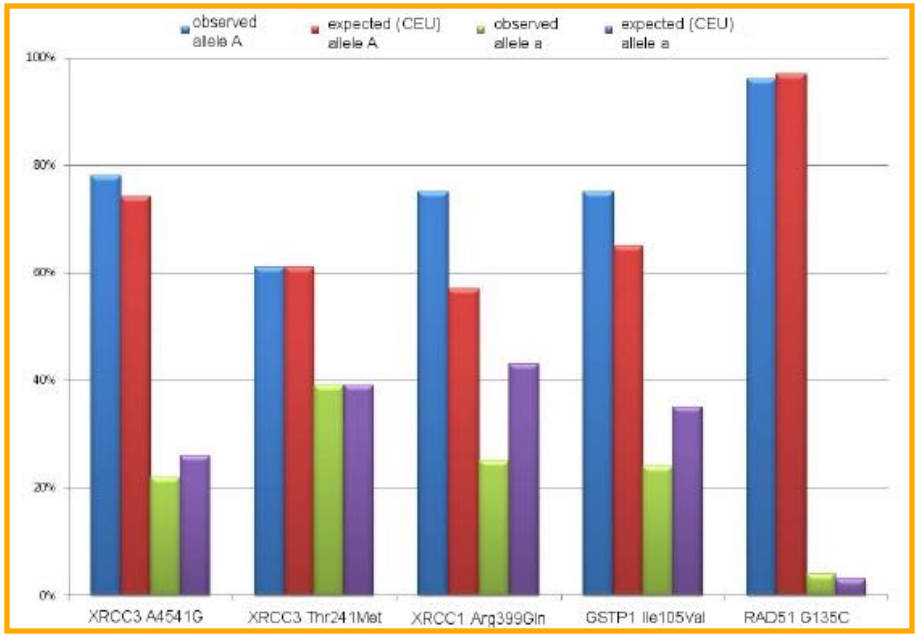
SNPs and toxicity

Results

Table 1 Main patient and tumor characteristics		
Age (years)	median (range)	66 (51-87)
Tumor stage	Tis/T1/T2	1/48/8
Nodal stage	N0/N1	54/3
Chemotherapy	yes/no	15/42
Hormone-therapy	yes/no	52/5
Follow-up (months)	median (range)	38 (19-50)

57 patients (March 2006 - January 2008)

Polymorphism distribution:
Allele frequencies comparable to those reported for European populations



Falvo et al. *Journal of Experimental & Clinical Cancer Research* 2012, 31:7

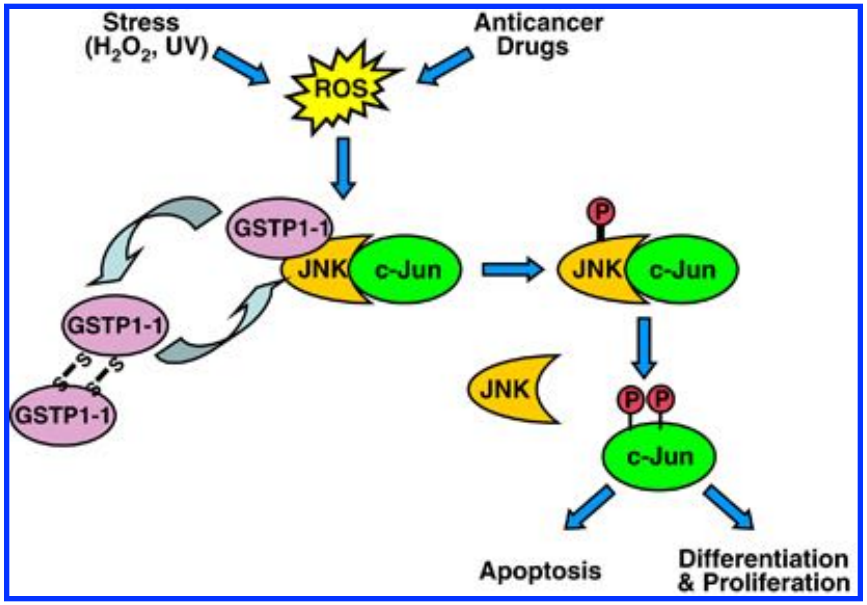
SNPs and toxicity

Results

Polymorphisms	Genotype	≥ G2 fibrosis or fat necrosis	OR (95% CI)	*p*-value (*)	*p*-value (§)
GSTP1	AA	38%	1		
	aa/Aa	64%	2.9 (0.88-10.14)	**0.047**	0.064

Subcutaneous fibrosis (≥ G2) or fat necrosis more frequent (64% vs 38%) in patients with the mutation or heterozygote genotype of **GSTP1** (OR = 2.9; p = 0.047).

No statistical significant increase/decrease of ORs was observed with *other SNPs* or their combination.



SNPs and toxicity

Conclusion

…. this study ... has a power of the study statistically sufficient to suggest that **SNP in GSTP1 gene** could be useful to predict late toxicity in BC patients who underwent SSPBI.

...future research will focus on the performance of many additional SNPs in other genes that are associated with the development of radiation toxicity…

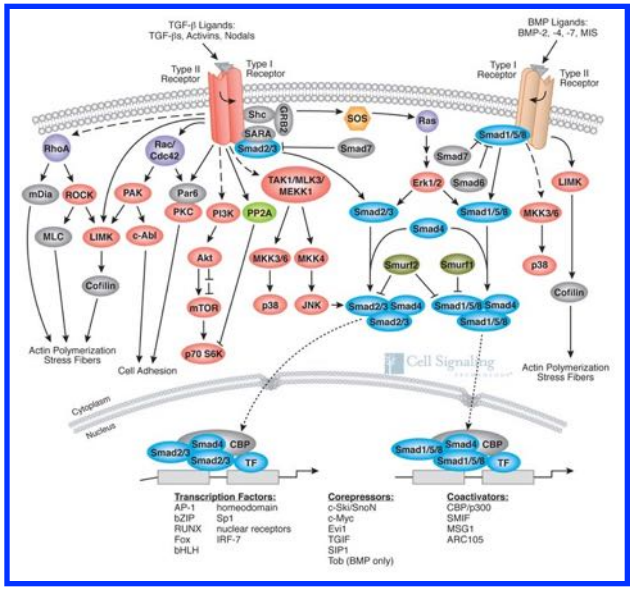
Falvo et al. *Journal of Experimental & Clinical Cancer Research* 2012, 31:7

SNPs and toxicity

Late toxicity

Individual patient data meta-analysis shows no association between the SNP rs1800469 in TGFB and late radiotherapy toxicity

To overcome publication bias, the international Radiogenomics Consortium collected and analysed individual patient data from both published and unpublished studies on **SNPs** in ***TGFB1*** (rs1800469 c.-1347T>C) and radiation-induced normal tissue injury



Barnett GC et al. *Radiotherapy and Oncology* 2012, 105: 289–295

SNPs and toxicity

Materials and methods

- **3257** patients with *breast cancer* (from 21 different cohorts, from members of the international *Radiogenomics Consortium*)
  - Patient-related factors: age, smoking status, body mass index (BMI), breast volume and the presence of co-morbidity such as diabetes mellitus and hypertension
  - Treatment-related factors: total dose, number of fractions, use of a radiotherapy boost, chemotherapy, hormone-therapy, acute toxicity, post-operative infection and surgical cosmesis
- SNPs studied in TGFB1: **rs1800469** c.-1347T>C
- Univariate analysis and multivariate analyses were performed

Barnett GC et al. *Radiotherapy and Oncology* 2012, 105: 289–295

SNPs and toxicity

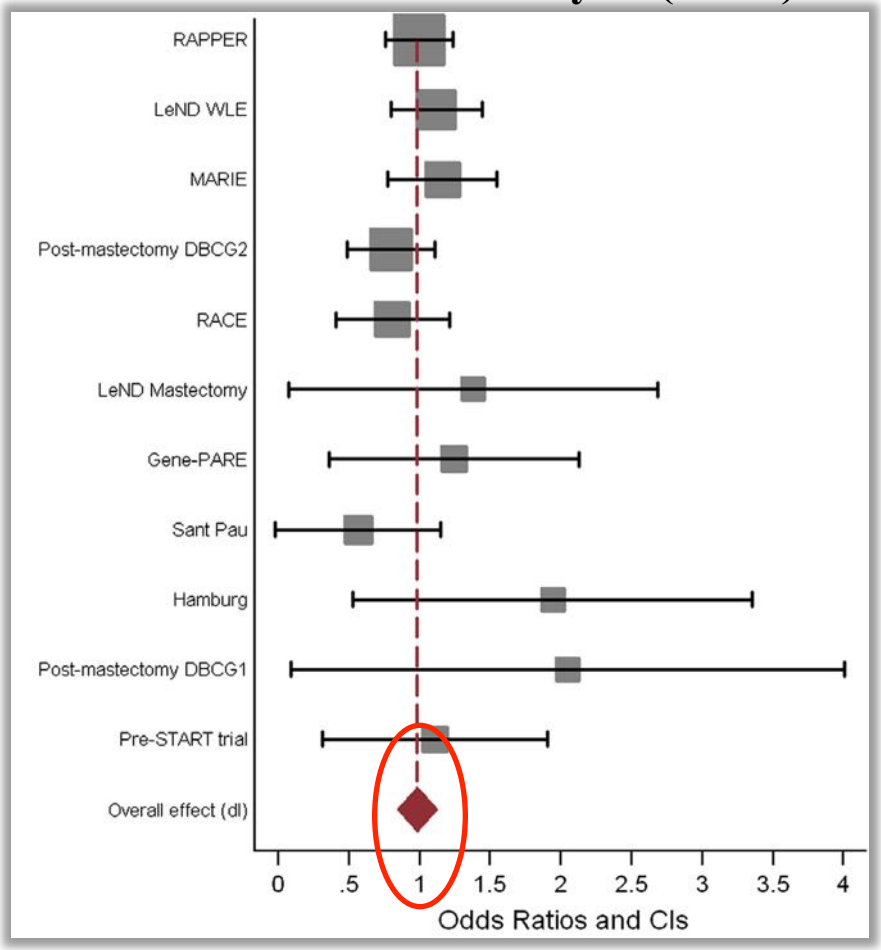
Results

Univariate analysis (UVA)

Study	*n* (UVA)	OR (UVA)	SE (UVA)
RAPPER	786	0.99	0.11
LeND WLE	480	1.13	0.17
MARIE	389	1.24	0.21
Post-mastectomy DBCG 2	234	1.00	0.17
RACE	161	0.75	0.18
LeND mastectomy	132	1.45	0.72
Gene-PARE	92	1.24	0.45
Sant Pau	78	0.67	0.32
Hamburg	69	1.94	0.72
Post-mastectomy DBCG 1	41	1.19	0.49
Pre-START trial	52	1.13	0.41

OR = 1.015 (95% CI 0.89, 1.14)
p = 0.67

Multivariate analysis (MVA)



Barnett GC et al. *Radiotherapy and Oncology* 2012, 105: 289–295

SNPs and toxicity

Conclusion

The meta-analysis demonstrates successful collaboration of groups included in the Radiogenomics Consortium…

…. this relatively large meta-analysis, found **no clinically relevant** association between the frequently-studied candidate SNP rs1800469 in TGFB1 and the development of fibrosis or other late radiotherapy toxicity…

Barnett GC et al. *Radiotherapy and Oncology* 2012, 105: 289–295

Molecular subtypes and efficacy

Triple Negative Breast Cancer Is Associated With an Increased Risk of Residual Invasive Carcinoma After Lumpectomy

Shirin Sioshansi, MD[1,2]; Shahrzad Ehdaivand, MD, MPH[3,4,5]; Christina Cramer, MD[4]; Michele M. Lomme, MD[3,4]; Lori Lyn Price, MAS[6]; and David E. Wazer, MD[3,7,8,9]

... to assess the **risk of residual carcinoma** related to multiple pathologic factors, including molecular phenotype...

Sioshinashi S et al. *Cancer* 2012;118:3893-8.

Molecular subtypes and efficacy

Materials and methods

- Retrospective review of pathologic records (369 pts)
- Invasive breast cancer who were treated with lumpectomy followed by a **second ipsilateral breast surgery**
- Data were collected on age, tumor size, grade, mitotic count, status of margins, lymph nodes, ER, PR, and Her2, as well as presence of EIC, lymphovascular invasion (LVI), multifocality.
- Patients with residual **DCIS** and **neoadjuvant** chemotherapy were excluded
- Univariate analysis and multivariate analyses were performed

Sioshinashi S et al. *Cancer* 2012;118:3893-8.

Molecular subtypes and efficacy

Results

Variable	Luminal A and B (n=286)	Her2-enriched (n=16)	Triple negative (n=43)	*P*
Median age, y	59	57	50	.0008
Median tumor size, cm	1.5	1.2	1.6	.39
High grade	19%	86%	74%	<.0001
High mitotic count	10%	50%	56%	<.0001
Lymphovascular invasion	20%	19%	30%	.27
Extensive intraductal component	35%	63%	43%	.07
Multifocal	30%	31%	33%	.94
Positive surgical margins	38%	6%	30%	.02
Positive lymph nodes	32%	27%	40%	.55
Residual invasive carcinoma	30%	31%	51%	.02

TN phenotype more likely to have

residual invasive carcinoma - *younger population* - *high grade* - *high mitotic count*

Sioshinashi S et al. *Cancer* 2012;118:3893-8.

Molecular subtypes and efficacy

Results

Correlation with residual invasive disease

Variable	N	OR (95% CI)	P
Age ≥45 y	365	0.45 (0.27, 0.76)	.003
Tumor size, cm	366		<.0001
≤1.0		Reference	
1.1-2		3.00 (1.62, 5.54)	.0005
>2		5.70 (2.98, 10.93)	<.0001
Grade	346		
1		Reference	
2		1.32 (0.68, 2.55)	.41
3		2.63 (1.31, 5.27)	.007
Lymphovascular invasion	367	2.56 (1.53, 4.28)	.004
Multifocal	367	1.78 (1.12, 2.85)	.02
Positive surgical margin	363	1.76 (1.12, 2.76)	.01
Positive lymph node	345	3.69 (2.29, 5.97)	<.0001
TN (vs non-TN)	343	2.48 (1.30, 4.74)	.006

Univariate Analysis

Multivariate logistic regression analysis

Variable	OR (95% CI)	P
TN (vs non-TN)	3.28 (1.56-6.89)	.002
Positive lymph node	3.06 (1.77-5.30)	<.0001
Tumor size 1.1-2.0 cm vs <1.0 cm	1.89 (0.94-3.82)	.076
Tumor size >2.0 cm vs <1.0 cm	3.49 (1.65-7.38)	.001

statistical significance

nodal status (OR: 3.06, P < .0001)

TN status (OR: 3.28, P = .002)

tumor size (OR: 3.49, P = .001)

Sioshinashi S et al. *Cancer* 2012;118:3893-8.

Molecular subtypes and efficacy

Conclusion

... study shows that **TN phenotype** is independently correlated with increased **risk of residual disease** after lumpectomy…

This finding suggests that **TNBCs** harbor more microscopic residual disease after lumpectomy … molecular phenotype should factor into decision-making regarding the extent of initial surgery … TNBCs may also benefit from dose escalation to the tumor bed region

Sioshinashi S et al. *Cancer* 2012;118:3893-8.

Molecular subtypes and efficacy

Low p53 Binding Protein 1 (53BP1) Expression Is Associated With Increased Local Recurrence in Breast Cancer Patients Treated With Breast-Conserving Surgery and Radiotherapy

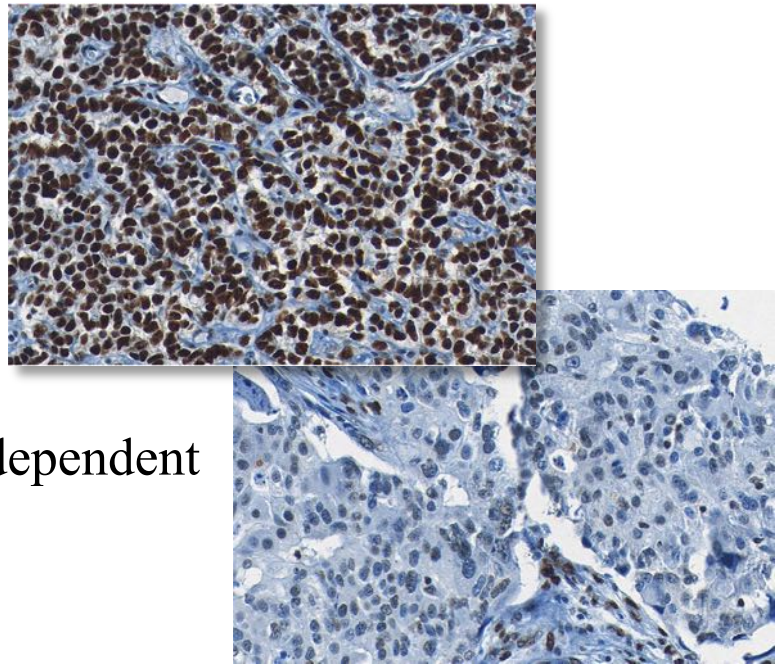
... to determine the clinical significance of **P53 binding protein 1 (53BP1) expression** for *local outcome* ... in a cohort of women with early-stage breast cancer treated with breast-conserving surgery and radiotherapy...

Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

Molecular subtypes and efficacy

Materials and methods

- 477 patients with evaluable tumor cores for staining of 53BP1
- Histologic evidence of invasive breast carcinoma with early-stage (I/II) disease and treated with BCS + RT
- Immunohistochemical analysis performed on 5-mm-thick tissue sections
- IBRFS, RFS, OS calculated
- Multivariate analysis used to assess the independent contribution of each variable to survival



Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

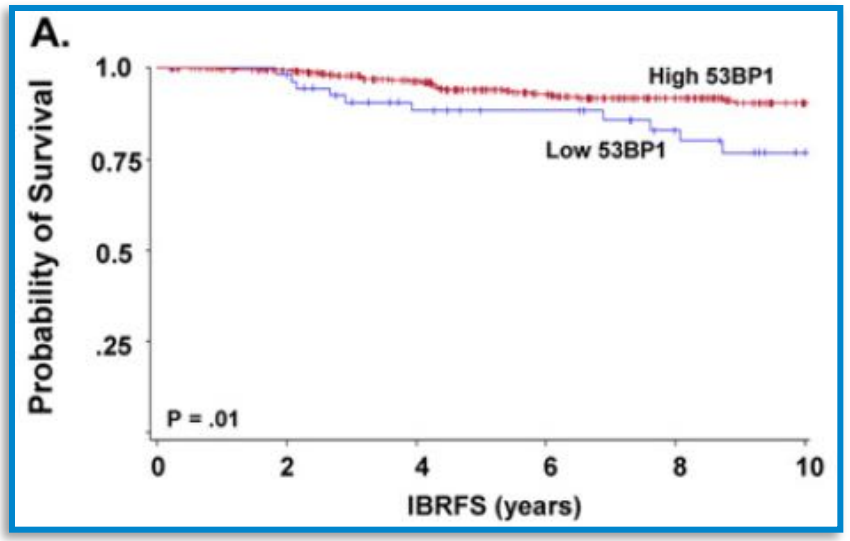
Molecular subtypes and efficacy

Results

Table 2 Ten-year survival as a function of 53BP1 expression

Outcome	53BP1 expression (% survival) Low	High	*P*
Ipsilateral breast recurrence–free survival	76.8	90.5	.01
Overall survival rate	66.4	81.7	.02
Cause-specific survival	66.0	87.4	<.01
Distant metastasis–free survival	55.9	87.0	<.01
Recurrence-free survival	45.2	80.6	<.01

IBRFS (76.8% vs. 90.5%; P=0.01)



Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

Molecular subtypes and efficacy

Results

Multivariate analysis for IBRFS

Prognostic factor	IBRFS	IBRFS HR (95% CI)
Age >50 y	0.4844	0.753 (0.341-1.666)
Race	0.4439	1.279 (0.682-2.399)
Tumor size	0.0076	2.546 (1.282-5.053)
Systemic therapy*	0.5639	0.807 (0.390-1.670)
Margin status	0.2744	1.175 (0.880-1.569)
ER status	0.2455	1.146 (0.911-1.442)
PR status	0.2862	0.896 (0.733-1.096)
HER2 status	0.7468	0.964 (0.772-1.204)
N stage	0.1549	1.097 (0.966-1.246)
53BP1 expression	0.0254	0.382 (0.164-0.888)

Low53BP1 expression and larger tumor size were found to be independently predictive of **worse IBRFS**

Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

Molecular subtypes and efficacy

Results

Outcome	Histological subtype (% survival)			
	Triple negative			
	53BP1 low	53BP1 high	Luminal*	$P^{\dagger}$
Ipsilateral breast recurrence–free survival	72.3	93.9	89.3	.036
Overall survival	59.5	89.8	78.1	.104
Cause-specific survival	63.4	85.5	85.3	.108
Distant metastasis–free survival	48.2	86.8	87.3	.004
Recurrence-free survival	37.8	83.7	80.0	.001

Low53BP1 expression *among triple-negative* was associated with **worse IBRFS**

High 53BP1 expression was associated with similar or better outcomes when *compared with the luminal patients*

Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

Molecular subtypes and efficacy

Conclusions

…Low53BP1 expression is an independent prognostic indicator for local relapse among other endpoints in early-stage breast cancer and TN breast cancer patients treated with BCS + RT.

… These results should be verified in larger cohorts of patients to validate their clinical significance.

Neboori HJR et al. *Int J Radiation Oncol Biol Phys,* 2012; 83:e677-83

Molecular subtypes and efficacy

Prognostic Value of Molecular Subtypes, Ki67 Expression and Impact of Postmastectomy Radiation Therapy in Breast Cancer Patients With Negative Lymph Nodes After Mastectomy

... To determine whether Ki67 expression and breast cancer subtypes could predict locoregional recurrence (LRR) and influence the *postmastectomy radiotherapy* (PMRT) decision in breast cancer (BC) patients with pathologic negative lymph nodes (pN0) after modified radical mastectomy (MRM)....

Selz J et al. *Int J Radiation Oncol Biol Phys,* 2012; 84:1123-32

Molecular subtypes and efficacy

Materials and methods

- 699 BC patients without lymph node involvement after mastectomy and axillary lymphadenectomy
- Patients with tumors overexpressing HER2 received adjuvant trastuzumab
- PMRT considered for each patient *during multidisciplinary staff meetings*
- Molecular subtypes according to IHC profile:
  - Luminal A (ER +, PR + and HER2-)
  - Luminal B (ER+, PR + and HER2+)
  - HER2 enriched (ER and PR - and HER2 +)
  - Basal-like or TN (ER - , PR - and HER2 -)

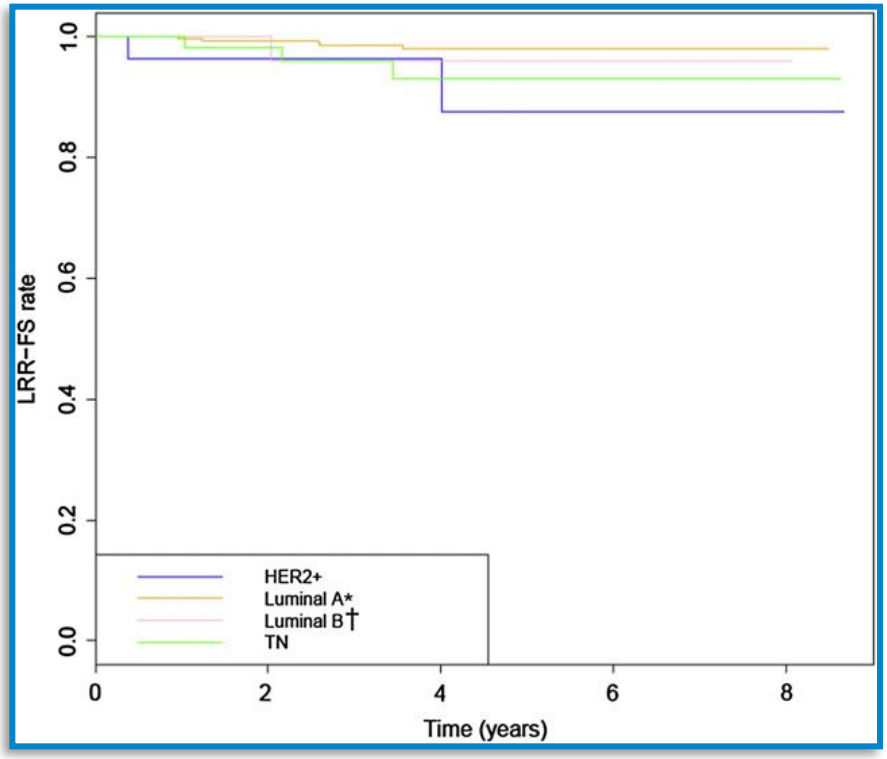
Selz J et al. *Int J Radiation Oncol Biol Phys,* 2012; 84:1123-32

Molecular subtypes and efficacy

Results

In multivariate analysis **Ki67 >20%** was the **only independent prognostic factor** associated with *increased LRR* (HR, 4.18; P<.0215)

None of the molecular subtypes was associated with the risk of LRR in MVA



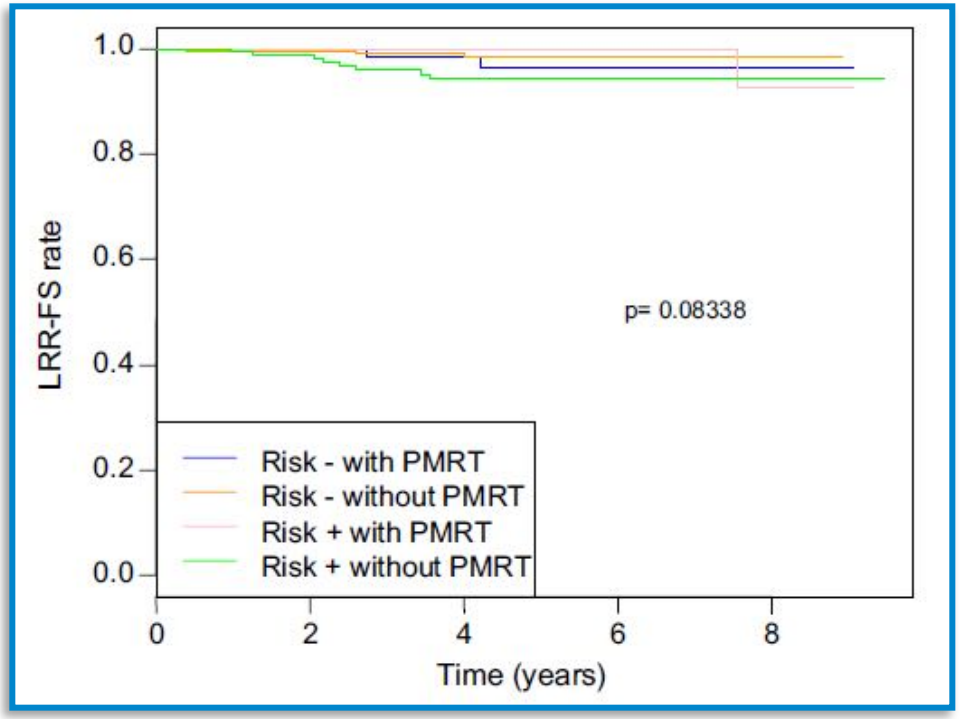
Selz J et al. *Int J Radiation Oncol Biol Phys,* 2012; 84:1123-32

Molecular subtypes and efficacy

Results

	PMRT group	Mo-PMRT group	
	5-year LRR-FS, % (95% CI)	5-year LRR-FS, % (95% CI)	*P*
Entire population	97.7 (95.2-100)	96.8 (95-98.5)	.663
Luminal A*	92.9 (87; 99.3)	93.3 (90.1; 96.6)	.8352
Luminal B†	80 (58.7; 100)	84.8 (69.6; 100)	.7256
HER2+‡	90 (73.2; 100)	78.2 (60.1; 100)	.3025
TN	89.4 (78.7; 100)	86.7 (77.2; 97.4)	.935
Risk +	90.7 (84.3; 97.6)	84.9 (79; 91.2)	.3512
Risk−	94.6 (88.7; 100)	97.4 (95.1; 99.7)	.1836

PMRT was not associated with a *higher rate of locoregional control* in the entire population or in the various subgroups of molecular subtypes



Selz J et al. *Int J Radiation Oncol Biol Phys,* 2012; 84:1123-32

Molecular subtypes and efficacy

Conclusions

… Ki67 expression but not BC molecular subtypes are predictive of locoregional recurrence in BC patients without lymph node involvement after modified radical mastectomy…

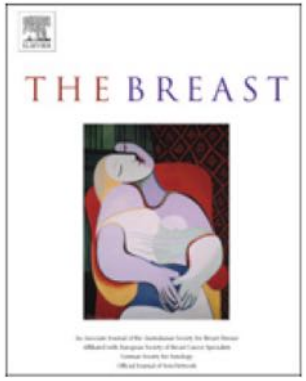
…The benefit of PMRT in the subgroup of patients with high risk of LRR defined by KI67 >20% should be further investigated in prospective studies…

Selz J et al. *Int J Radiation Oncol Biol Phys,* 2012; 84:1123-32

Molecular subtypes and efficacy

Original article

Predictive value of breast cancer molecular subtypes in Chinese patients with four or more positive nodes after postmastectomy radiotherapy



… To evaluate predictive value of breast cancer molecular subtypes in patients with *four or more positive nodes after postmastectomy radiotherapy*…

Wu S et al. *Breast,* 2012; 21:657-61

Molecular subtypes and efficacy

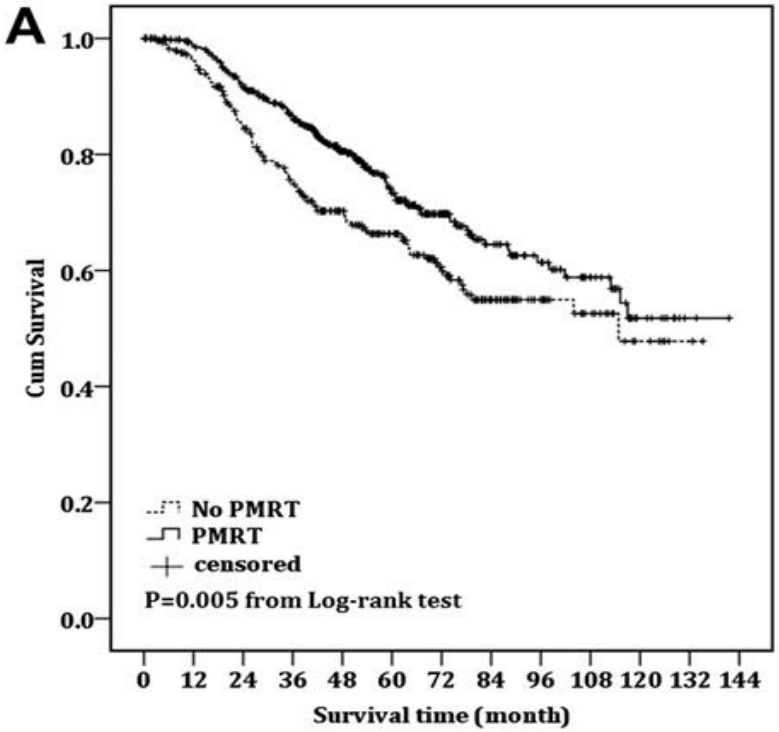
Materials and methods

- 774 patients with four or more positive nodes after mastectomy
- No patients received anti-HER2 treatment.
- 98% received chemotherapy
- A total of 475 patients (61.4%) were treated with PMRT within six months after mastectomy
- Endpoints: rates of locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival (OS).

Wu S et al. *Breast,* 2012; 21:657-61

Molecular subtypes and efficacy

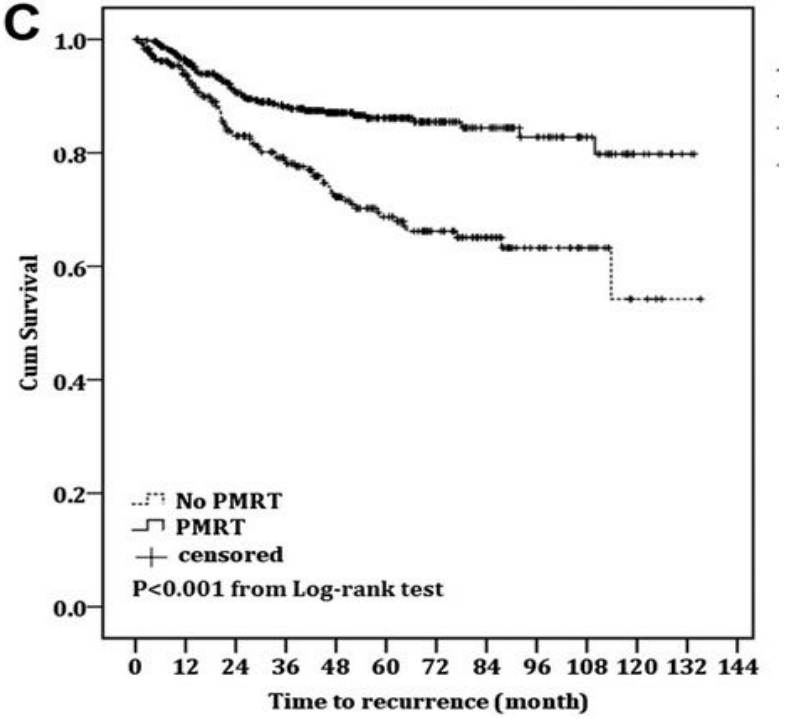
Results



5-year OS: 70% PMRT vs 60% no PMRT
P=0.005

5-year RFS: 85% PMRT vs 67% no PMRT
P<0.001

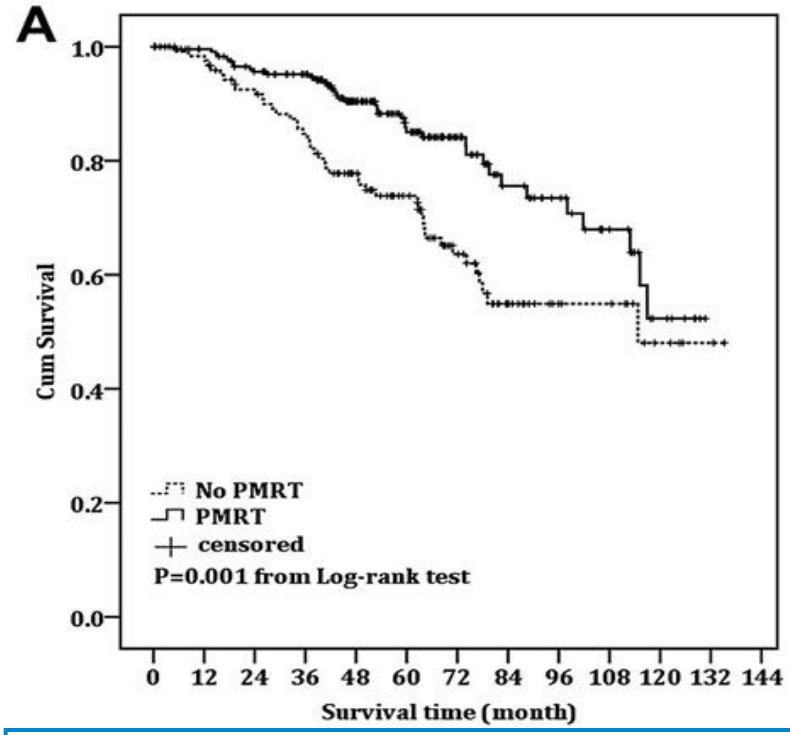
All patients



Wu S et al. *Breast,* 2012; 21:657-61

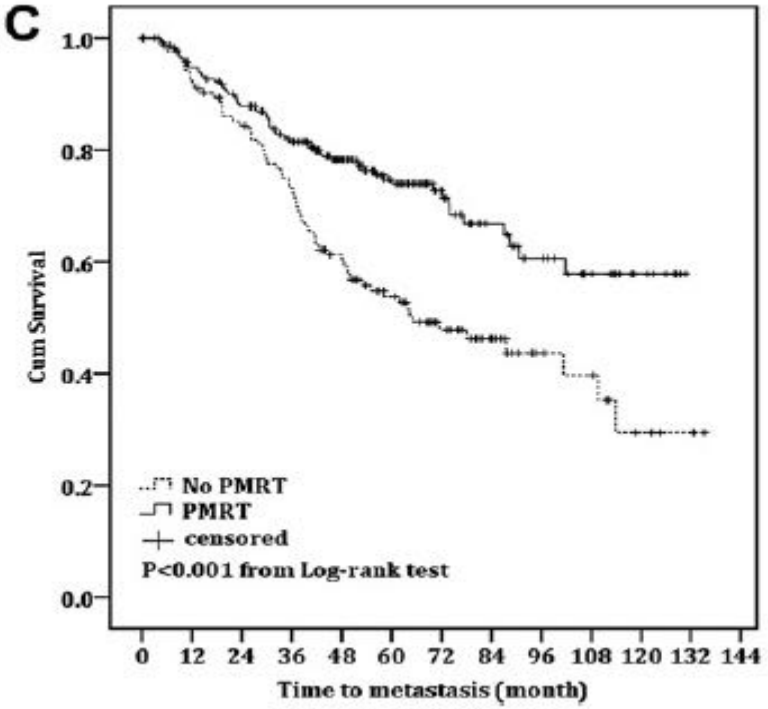
Molecular subtypes and efficacy

Results



5-year RFS: 93% PMRT vs 66% no PMRT (P<0.001)

Luminal A



5-year OS: 84% PMRT vs 63% no PMRT P=0.001

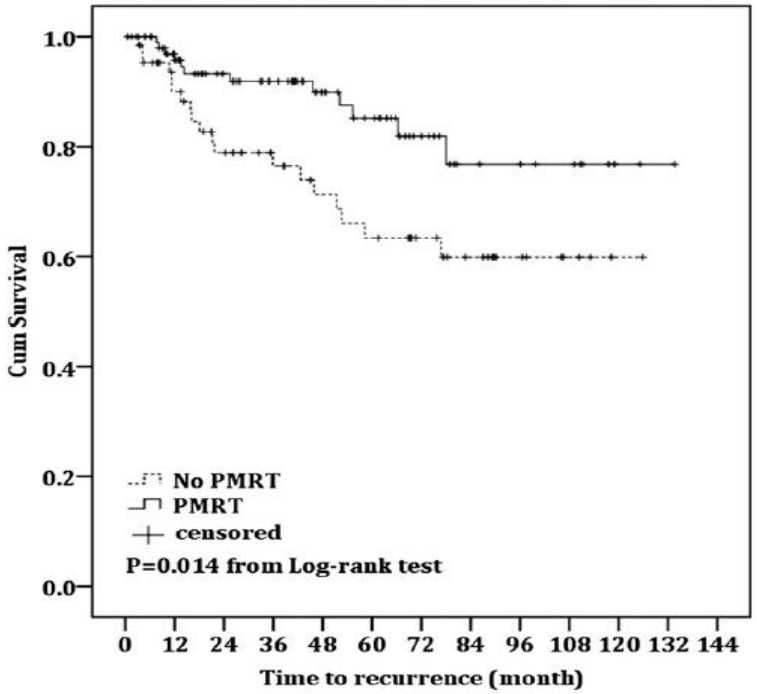
Wu S et al. *Breast,* 2012; 21:657-61

Molecular subtypes and efficacy

Results

5-year RFS: 77% PMRT vs 64% no PMRT (P=0.014)

Luminal B



Characteristic	Her2-enriched[b]		
	PMRT ($n = 72$)	Non-PMRT ($n = 63$)	*P* value
Tumor stage			0.182
T1–T2	47 (65.3)	48 (76.2)	
T3–T4	25 (34.7)	15 (23.8)	
N stage			0.892
N2	40 (55.6)	34 (54.0)	
N3	32 (44.4)	29 (46.0)	
Mortality	39 (54.2)	34 (54.0)	0.995
Metastasis	39 (54.2)	34 (54.0)	0.990
Recurrence	15 (20.8)	10 (15.9)	0.616

Characteristic	Basal-like[a]		
	PMRT ($n = 66$)	Non-PMRT ($n = 39$)	*P* value
Tumor stage			0.162
T1–T2	46 (69.7)	32 (82.1)	
T3–T4	20 (30.3)	7 (17.9)	
N stage			0.081
N2	29 (43.9)	24 (61.5)	
N3	37 (56.1)	15 (38.5)	
Mortality	38 (57.6)	20 (51.3)	0.531
Metastasis	39 (59.1)	19 (48.7)	0.302
Recurrence	15 (22.7)	11 (28.2)	0.530

Wu S et al. *Breast,* 2012; 21:657-61

Molecular subtypes and efficacy

Conclusions

… different molecular subtypes of breast cancer have different prognoses and distinct sensitivities to PMRT

Wu S et al. *Breast,* 2012; 21:657-61

Molecular subtypes and efficacy

Brain metastases from breast cancer: proposition of new prognostic score including molecular subtypes and treatment

… to develop a specific prognostic score for BC patients with brain metastasis, taking into account general and *specific biological factors*, the *molecular subtype* of BC, and *specific treatment parameters*, in order to help define homogeneous cohorts for prospective randomized trials …

Le Scodan R et al. *J Neurooncol,* 2012; 106:169–176

Molecular subtypes and efficacy

Materials and methods

- 130 patients with brain metastasis (BM) who received whole-brain RT
- Survival curves were constructed with the Kaplan–Meier method and compared with the log-rank test
- Univariate (Cox regression model) and multivariate analysis was used to test the *following variables* for their impact on overall survival: age at BM diagnosis, KPS, RTOG RPA class, presence of extracranial metastases, sites of other extracranial metastases, number of BM, interval between primary tumor and BM diagnosis, tumor HR status, HER-2 overexpression, trastuzumab-based therapy and the BC molecular subtype

Le Scodan R et al. *J Neurooncol,* 2012; 106:169–176

Molecular subtypes and efficacy

Covariate	Comparison	Hazard ratio (CI 95%)	P ($n = 130$)
Brain metastases	Presence of systemic metastases vs. alone	1.52 (0.62; 3.74)	0.366
Visceral metastases	Yes vs. no	1.34 (0.84; 2.11)	0.2159
Bone metastases	Yes vs. no	1.07 (0.71; 1.60)	0.745
KPS	>70 vs. <70	0.51 (0.34; 0.77)	0.0013
Age at BM diagnosis	≥50 vs. <50	1.21 (0.80; 1.81)	0.329
Histology	Lobular and other vs. Ductal	0.77 (0.34; 1.77)	0.545
Tumor HR status	Negative vs. positive	1.37 (0.91; 2.06)	0.127
HER-2 overexpression	Negative vs. positive	1.48 (0.98; 2.24)	0.0606
HR− & HER2−	Yes vs. no	2.17 (1.38; 3.43)	0.0006
HR± & HER2+	Yes vs. no	1.51 (0.99; 2.29)	0.0521
HR+ & HER2−	Yes vs. no	1.17 (0.77; 1.79)	0.4667
Trastuzumab-based therapy for HER2 overexpressing tumor	Yes vs. no	0.45 (0.27; 0.75)	0.001631
SBR grade	3 vs. 1–2	1.59 (1.00; 2.52)	0.0484
LDH (U/l)	>500 vs. ≤500	2.01 (1.27; 3.16)	0.0026
Lymphocyte count	>700 vs. ≤700	0.58 (0.37; 0.89)	0.0138
Time interval (year) between primary tumor and BM diagnosis	≥2 vs. <2	3.76 (0.52; 27.18)	0.968
No. of BM	Multiple vs. single	1.12 (0.41; 3.06)	0.822
Total radiation dose (Gy)	>30 vs. ≤30	1.54 (0.49; 4.91)	0.463
RTOG RPA class	III vs. I–II	1.98 (1.32; 2.98)	0.0013

Univariate analysis

- KPS <70
- RTOG RPA Class III
- trastuzumab-based therapy for HER- 2 +
- triple-negative phenotype
- serum LDH level
- lymphocyte count at BM diagnosis

were predictive of overall survival

Le Scodan R et al. *J Neurooncol,* 2012; 106:169–176

Molecular subtypes and efficacy

Entire population ($n = 130$)			7.43 (5.52;9.73)	54.9 (46.8; 64.3)	35.8 (28; 45.7)
BMBC RPA Class I good-prognosis group ($n = 32$)	Patients with HER2-overexpressing tumors treated with trastuzumab	1	19.53 (9.27; Inf)	77.1 (63.5; 93.6)	62.6 (47.2; 83)
BMBC RPA Class II intermediate-prognosis group ($n = 61$)	Remaining patients	1.28 (0.7–2.35)	12.49 (8.58; 24.99)	66.4 (52.5; 83.9)	51.3 (37; 71.1)
BMBC RPA Class III poor-prognosis group ($n = 37$)	Patients not treated with trastuzumab and: lymphopenia at BM diagnosis or KPS <70 and ≥50 years at BM diagnosis or KPS ≥70 and triple-negative tumors	3.75 (2.15–6.52)	3.52 (3.09; 6.15)	36.5 (26.1; 51.1)	12.2 (5.7; 26)
		P value log rank <0.0001			

Best survival (median of 19.5 months) among pts HER2 + who received trastuzumab

Worst survival (median of 3.5 months) among pts who did not receive trastuzumab and who had lymphopenia at BM or KPS <70 and age over 50 years at BM diagnosis, or KPS ≥70 and a triple-negative tumor

Le Scodan R et al. *J Neurooncol,* 2012; 106:169–176

Molecular subtypes and efficacy

Conclusions

BM patients HER2+ treated with trastuzumab can expect a median overall survival time of about 20 months … this subgroup of patients may therefore have a higher risk of experiencing late radiation-related toxicity… and might benefit from longer-course WBRT with lower doses per fraction

… However, this specific prognostic score was developed in a selected population of patients with advanced disease … and for whom WBRT was considered to be the standard treatment... Therefore …prospective validation of this prognostic score is needed, and we encourage other investigators to validate it externally.

Le Scodan R et al. *J Neurooncol,* 2012; 106:169–176

Conclusions

❖No "robust" data show association between **toxicity RT-related** and molecular subtypes

❖TN phenotype is independently correlated with increased **risk of residual disease** *after lumpectomy (*..should factor into decision-making regarding the extent of initial surgery … TNBCs may also benefit from dose escalation to the tumor bed region*)*

❖Low53BP1 expression is a prognostic indicator for **local relapse** in *early-stage breast cancer and triple negative pts* treated with BCS + RT.

Conclusions

❖Ki67 expression but not molecular subtypes are predictive of locoregional recurrence in BC patients *without node involvement after radical mastectomy;* PMRT was not associated with a higher rate of locoregional control

❖Different molecular subtypes in patients with *four or more positive nodes after postmastectomy radiotherapy* have different prognoses and distinct sensitivities to PMRT (best outcome for luminal A e B, worse outcome for basal-like e Her2 enriched)

Conclusions

Genome-Wide Association Studies to investigate cancer risk, survival outcome, treatment-related toxicity, or predictive factors for treatment response.

Progress in this field of research requires collaboration and cooperative groups to standardize methodologies and facilitate data sharing (national and international biorepositories)