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A.O. Spedali Civili di Brescia

Incontri Bresciani di Radioterapia Oncologica – Edizione 2011
Brescia Meetings in Radiation Oncology – 2011 Edition

BREAST CANCER:
TOWARD A PATIENT-CENTERED PERSPECTIVE

Brescia – September 30th, 2011

Con il Patrocinio di:

Università degli Studi di Brescia – Facoltà di Medicina e Chirurgia
A.O. Spedali Civili di Brescia
XVIII DIPO – Dipartimento Oncologico Provinciale Bresciano
AIRO – Associazione Italiana di Radioterapia Oncologica
AIRO – Gruppo Regionale Lombardia
AIRO Giovani
AIRB – Associazione Italiana di Radiobiologia
AIOM – Associazione Italiana di Oncologia Medica

Predictors of late Toxicity

Marco Krengli

AMEDEO AVOGADRO
università degli studi del piemonte orientale

Does variability in normal tissue reactions after radiotherapy have a genetic basis – where and how to look for it?

Christian Nicolaj Andreassen*, Jan Alsner, Jens Overgaard

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Radiother Oncol 64(2002):131 - 140

- Late toxicity after radiation is a multifactorial event.

- Patient characteristics and technical factors can influence the incidence of late effects.

But:

- Patients with similar characteristics and treated with homogenous techniques may develop a different spectrum and various levels of toxicity.

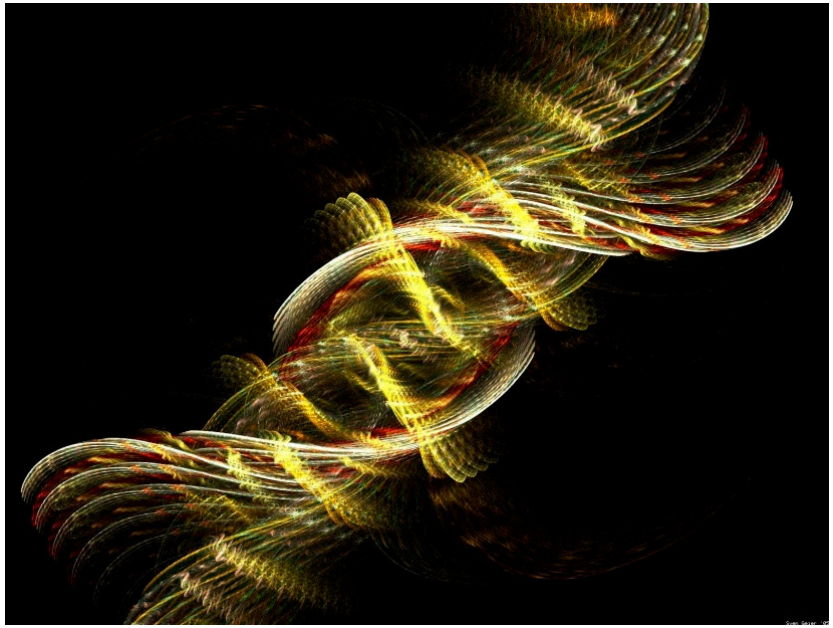
Genetic factors ?

The Cambridge Breast Intensity-modulated Radiotherapy Trial: Patient- and Treatment-related Factors that Influence Late Toxicity

Barnett et al Clinical Oncol, 2011 in press

Multivariate analysis at 2 years in 1,014 pts

End point	Variable	Odds ratio	95% confidence interval	*P* value
Assessment by serial photographs				
Breast shrinkage	Breast volume	1.98†	1.41, 2.78	<0.0005
	Vol >107%*	1.55	1.06, 2.26	0.023
	Boost	1.33	0.93, 1.91	0.12
Overall cosmesis	Breast volume	1.38†	0.92, 2.08	0.13
	Surgical cosmesis	37.23	21.5, 64.3	<0.0005
	Vol >107%*	1.60	0.97, 2.63	0.066
	Boost	1.27	0.80, 2.02	0.32
Clinical assessment				
Telangiectasia	Breast volume	3.94†	2.49, 6.24	<0.0005
	Age	1.32‡	0.97, 1.79	0.076
	Specimen weight	1.037§	1.0089, 1.067	0.010
	Postoperative infection	3.39	1.94, 5.91	<0.0005
	Vol >107%*	1.97	1.055, 3.68	0.033
Breast oedema	Breast volume	3.65†	2.54, 5.24	<0.0005
	Age	1.44‡	1.18, 1.76	<0.0005
	Diabetes mellitus	1.64	0.77, 3.50	0.20
	Boost	1.71	1.20, 2.43	0.003
	Acute response	1.51‖	1.13, 2.02	0.006
Breast shrinkage	Breast volume	1.26†	0.91, 1.77	0.17
	Diabetes mellitus	2.08	0.73, 1.10	0.10
	Specimen weight	1.0054§	0.98, 1.04	0.73
	Surgical cosmesis	4.16	3.07, 5.66	<0.0005
Any induration	Surgical cosmesis	2.23	1.57, 3.19	<0.0005
	Boost	1.93	1.27, 2.93	0.002
Pigmentation	Breast volume	1.75†	1.21, 2.51	0.003
	Smoking status	2.06	1.22, 3.49	0.007
Patient reported				
Breast pain	Boost	1.38	1.04, 1.83	0.026
	Breast volume	1.29†	0.98, 1.70	0.073
	Age	0.81‡	0.70, 0.94	0.007
Oversensitivity	Postoperative infection	1.78	1.27, 2.49	0.001
	Acute response	1.29‖	1.02, 1.64	0.036



- Patients affected by rare genetic syndromes such as ataxia teleangectasia, Nijmegen breakage syndrome, Fanconi's anaemia and Bloom's syndrome experience more severe toxicity than general population.

- In the beginning, most attention was paid to ATM, BRCA1, BRCA2 and mutations.

- Then, it was hypothesized that single nucleotide polymorphisms (SNPs), the most abundant type of sequence variation in the human genome, could make up a proportion of the genetic background (Andreassen, 2005).

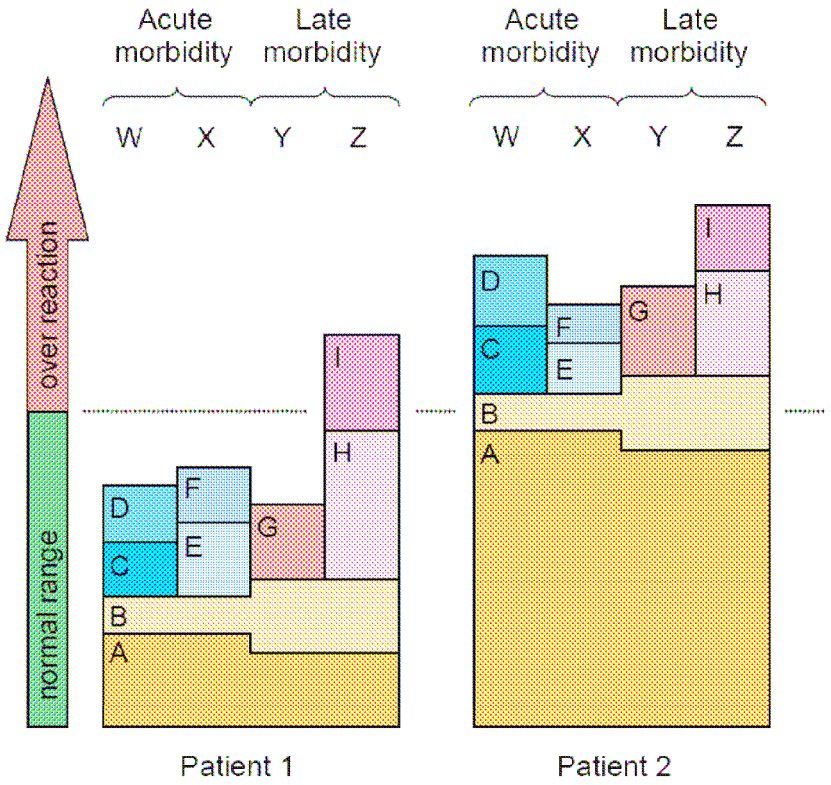
REVIEW ARTICLE

Can risk of radiotherapy-induced normal tissue complications be predicted from genetic profiles?

CHRISTIAN NICOLAJ ANDREASSEN

Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

Acta oncologica 44(2005):801 - 815



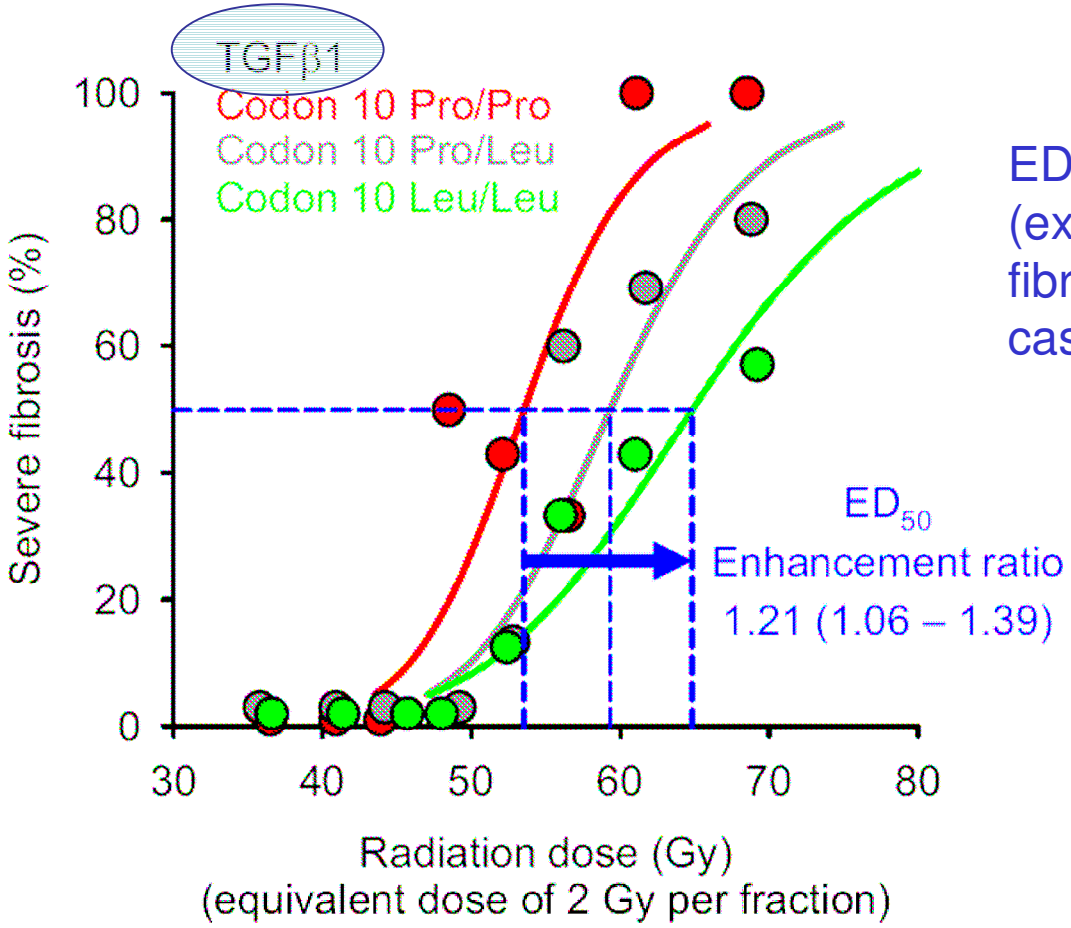
- Mutations of genes expressed only in some tissues can affect only the radiosensitivity of such tissue.

- Mutations of genes expressed in all tissues can affect the radiosensitivity of all tissues.

Genetic Markers for Prediction of Normal Tissue Toxicity After Radiotherapy

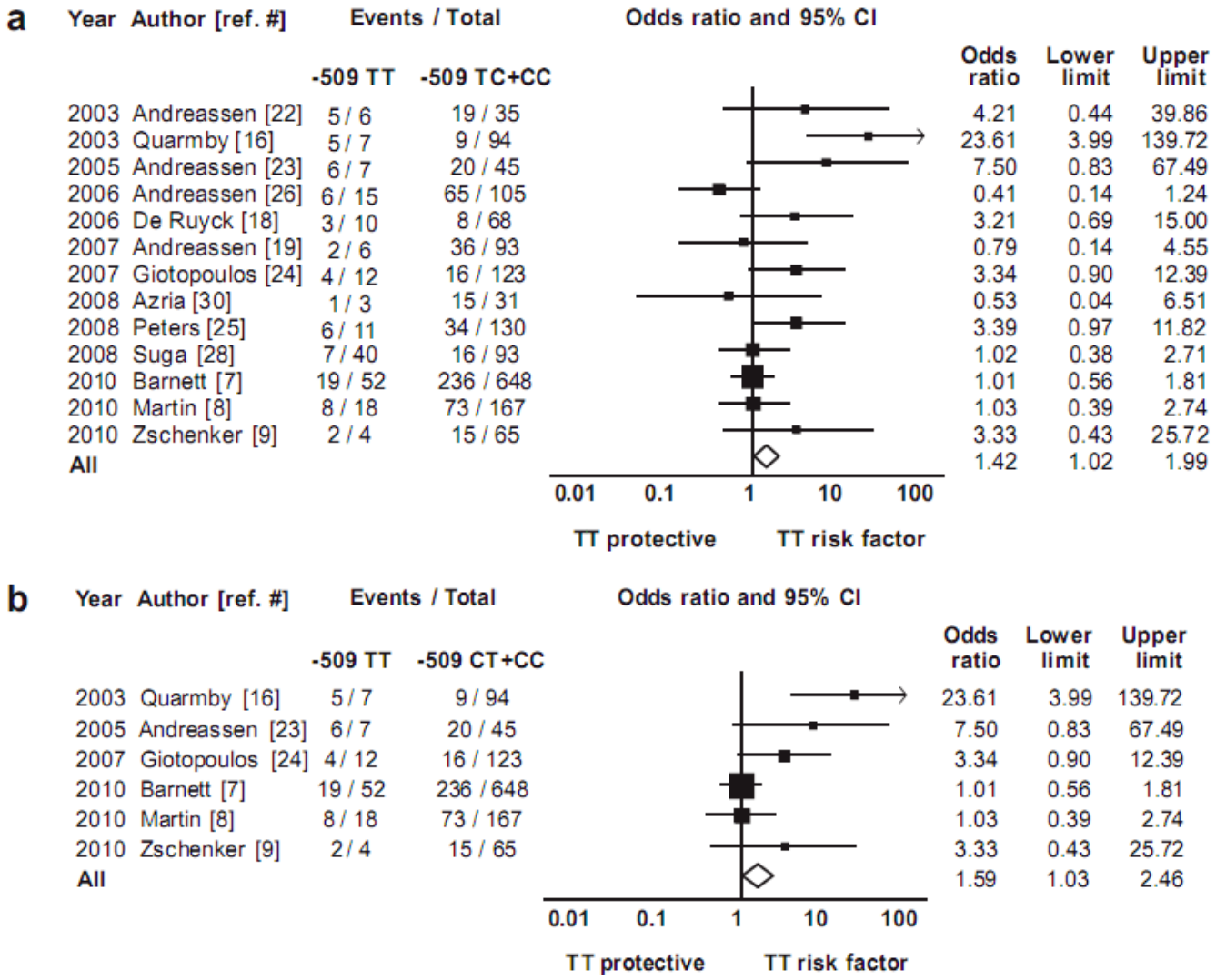
Jan Alsner, PhD, Christian Nicolaj Andreassen, MD, PhD, and
Jens Overgaard, MD, DMSc, FRCR, FACR

Semin Radiat Oncol 2008(18):126 - 135



ED_{50} = effective dose (expected to cause fibrosis in 50% of cases)

Meta-analysis of studies addressing the impact of the TGFB1 position 509 C/T SNP upon risk of various late normal tissue reactions (a) and risk of late toxicity in the breast (b).



Andreassen CN, Radiother Oncol 2010; 97: 1-8

Observational Study CE 117/09

Polymorphic variants of genes predicting acute and late toxicity in patients who underwent postoperative radiotherapy after conservative surgery for breast cancer.

Radiotherapy, DMCS e BRMA, and Laboratory of Pharmacogenetics, DISCAFF, University of "Piemonte Orientale"

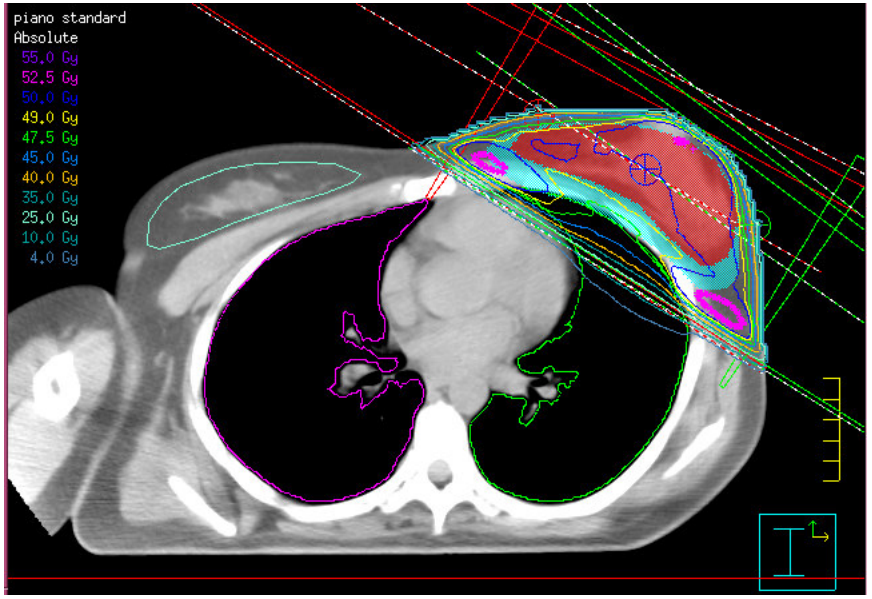
Inclusion criteria:

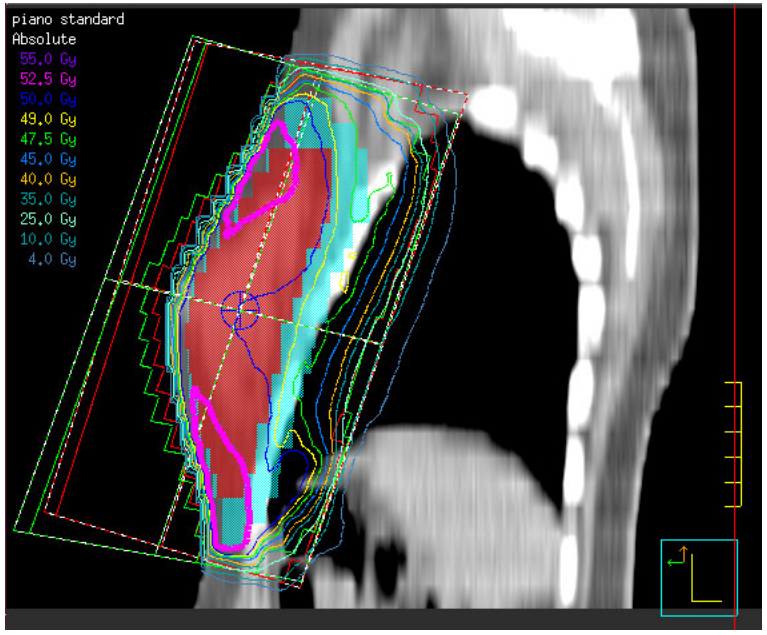
- Conservative surgery (96% quadrantectomy) from 1989 through 2009 with or without adjuvant chemotherapy/hormontherapy

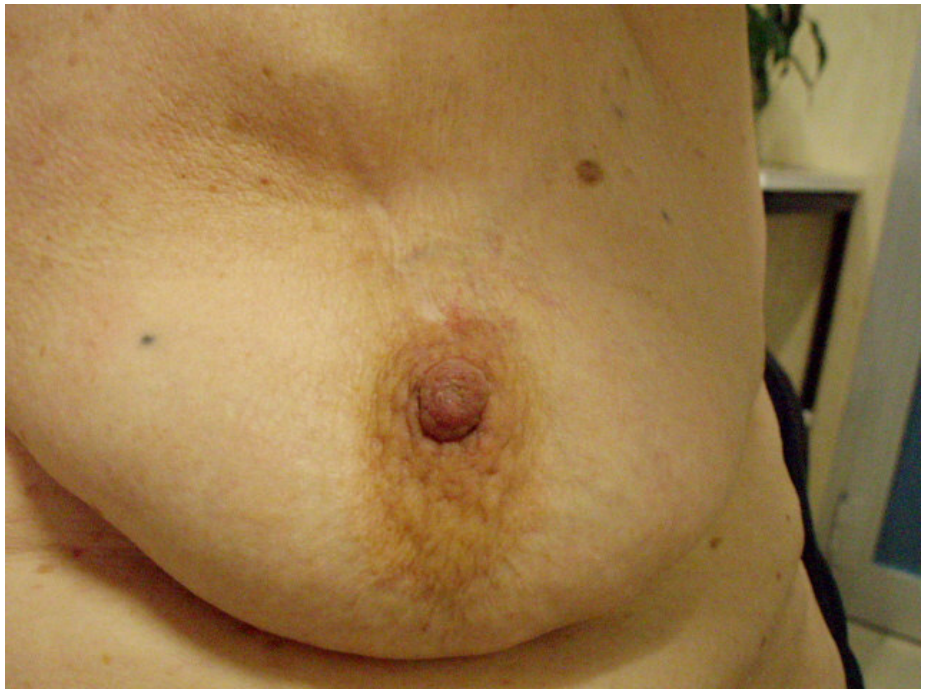
Radiotherapy:

- Two opposed tangential fields on CT slices for planning
- Dose to ICRU of 45 – 50,4 Gy, fxs 1,8 – 2Gy/die;
- Boost to tumour bed of 9 – 16 Gy.

Radiation Therapy and example of late toxicity







Grade 3 fibrosis (SOMA LENT)

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Common Variants of GSTP1, GSTA1, and TGFβ1 are Associated with the Risk of Radiation-Induced Fibrosis in Breast Cancer Patients

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Analysis of 237/257 pts

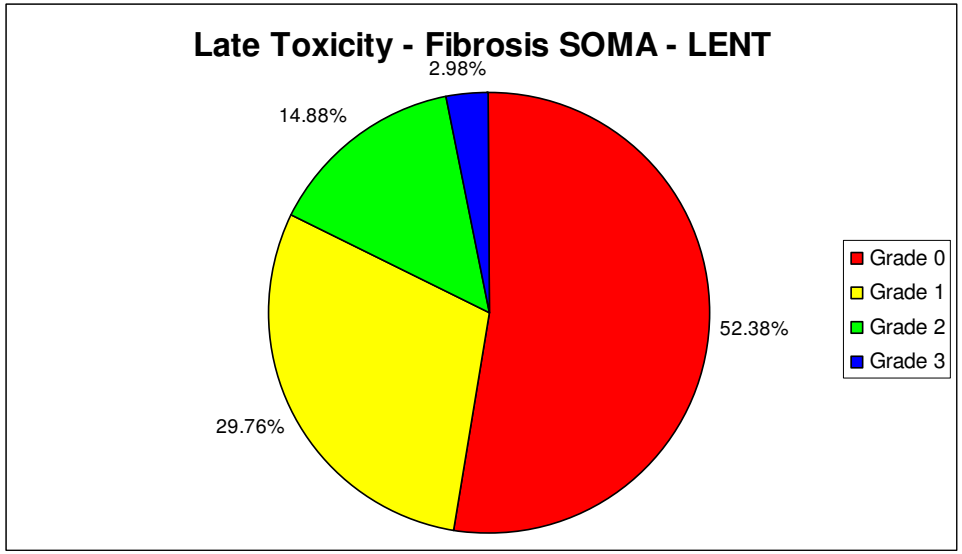


Table 3 Distribution of polymorphic variants in the study population

Polymorphism	Patients, *n* (%)	*p* value*
XRCC1 Arg399Gln		0.603
Arg/Arg	95 (39.9)	
Arg/Gln	113 (47.5)	
Gln/Gln	29 (12.2)	
XRCC1 Arg 194Trp		0.898
Arg/Arg	209 (87.8)	
Arg/Trp	27 (11.3)	
Trp/Trp	1 (0.4)	
ENOS G894T		0.452
GG	97 (40.8)	
GT	105 (44.1)	
TT	35 (14.7)	

XRCC1 and TP53

Base-excision repair mechanisms

GSTP1, GSTA1 and eNOS

Oxidative stress response

TGFß1

Fibroblast proliferation and differentiation

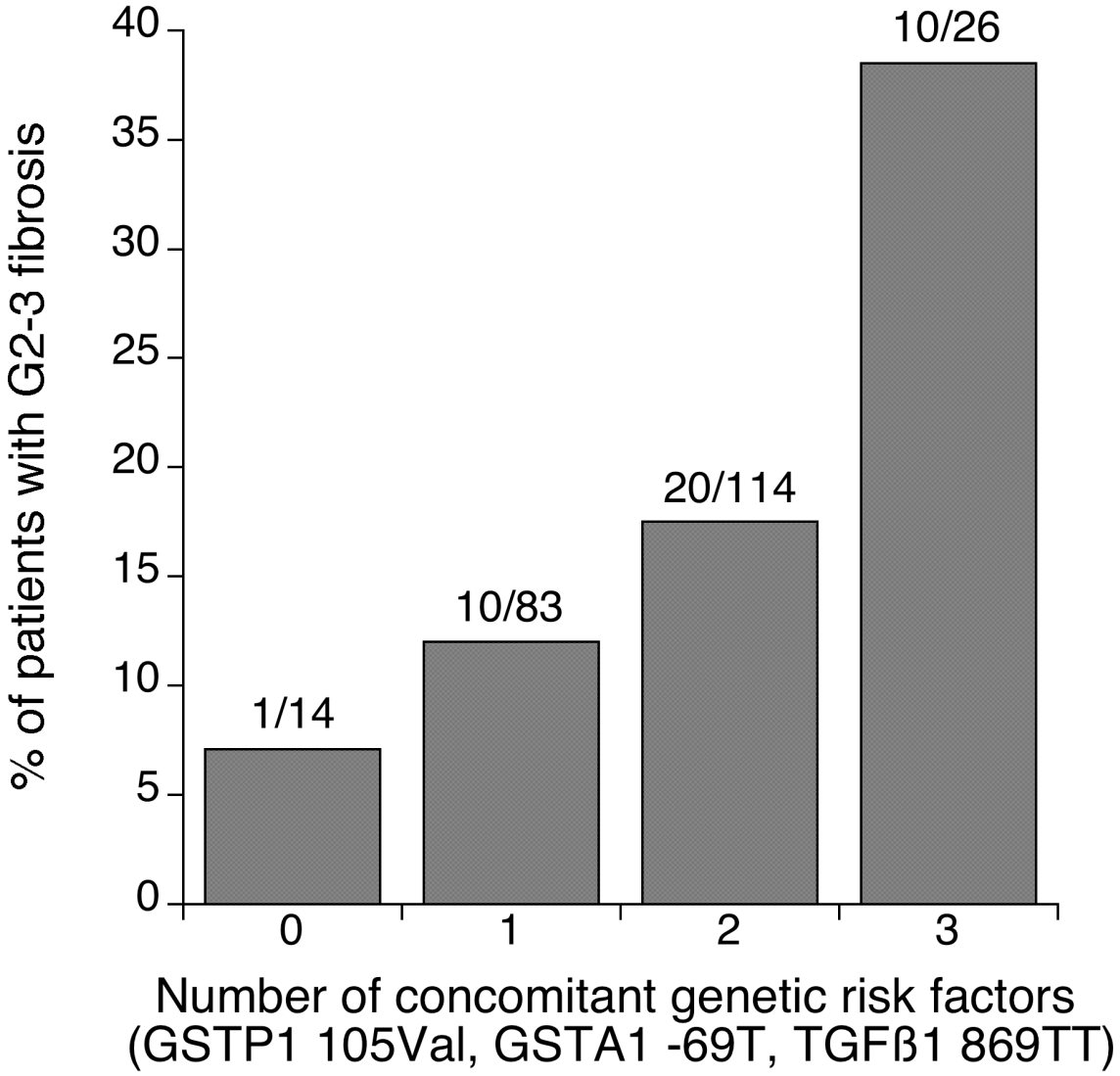
Table 2 Clinical and demographic characteristics in the whole set of breast cancer patients ($n = 237$) and after stratification according to the radiosensitive status (LENT-SOMA Grade 2–3 fibrosis in 41 patients and Grade 0–1 fibrosis in 196)

Clinical variables	Total: $n = 237$ (%)	Grade 0–1: n (%)	Grade 2–3: n (%)	p value*
Age (y): median (range)	60 (35–85)			
Age (y): mean (SD)		60.2 (9.5)	63.9 (10.4)	0.040
BMI, median (range)	24.2 (18–51.4)			
BMI, mean (SD)		24.6 (3.9)	26.1 (3.8)	0.010
Breast diameter (cm): $n = 236$				
Median (range)	12 (4.9–25)			
Mean (SD)		12.0 (2.6)	12.94 (2.3)	0.011
Follow-up (mo): median (range)	63 (9–222)			
Follow-up, mean (SD)		70.2 (42.5)	72.9 (39.6)	0.413
Acute toxicity (RTOG Grade >1), $n = 236$				
No	161 (68.2)	132 (67.7)	29 (70.7)	0.704
Yes	75 (31.8)	63 (32.3)	12 (29.3)	
Diabetes				
No	222 (93.7)	186 (94.9)	36 (87.8)	0.090
Yes	15 (6.3)	10 (5.1)	5 (12.2)	
Hypertension				
No	176 (74.3)	146 (74.5)	30 (73.2)	0.861
Yes	61 (25.7)	50 (25.5)	11 (26.8)	
History of vasculopathy				
No	218 (92.0)	179 (91.3)	39 (95.1)	0.541
Yes	19 (8.0)	17 (8.7)	2 (4.9)	
Smoking status				
Never	200 (84.4)	162 (82.7)	38 (92.7)	0.108
Current or former	37 (15.6)	34 (17.3)	3 (7.3)	
Alcohol (wine at meals)				
No	229 (96.6)	189 (96.4)	40 (97.6)	1.000
Yes	8 (3.4)	7 (3.6)	1 (2.4)	
Adjuvant treatment, $n = 227$				
None	24 (10.6)	21 (11.2)	3 (7.5)	0.915
Chemotherapy (C)	51 (22.5)	42 (22.5)	9 (22.5)	
Hormone therapy (H)	107 (45.8)	87 (46.5)	20 (50.0)	
C + H	45 (19.8)	37 (19.8)	8 (20)	
Dose/fraction, Gy				
2	229 (96.6)	189 (96.4)	40 (97.6)	1.000
1.8	8 (3.4)	7 (3.6)	1 (2.4)	
Radiation quality				
x-rays	218 (92.0)	179 (91.3)	39 (95.1)	0.541
γ-rays	19 (8.0)	17 (8.7)	2 (4.9)	
Boost therapy type				
Electrons	202 (85.2)	168 (85.7)	34 (82.9)	0.886
Photons (x-rays)	14 (5.9)	11 (5.6)	3 (7.3)	
No boost	21 (8.9)	17 (8.7)	4 (9.8)	
Boost dose fractionation (Gy)				
3	59 (24.9)	50 (25.5)	9 (21.9)	0.883
1.5–2	157 (66.2)	129 (65.8)	28 (68.3)	
No boost	21 (8.9)	17 (8.7)	4 (9.8)	

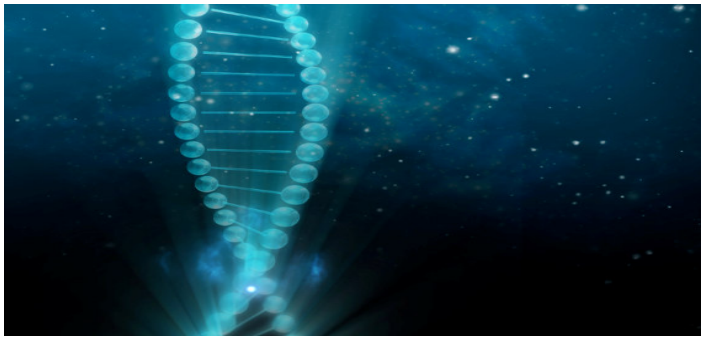
Table 4 Association between single-nucleotide polymorphisms and radiation-induced skin fibrosis in breast cancer patients

Polymorphism	Grade 0–1 *n* (%)	Grade 2–3 *n* (%)	Odds ratio*	95% confidence interval	*p* value
XRCC1 Arg399Gln					
Arg/Arg	77 (39.3)	18 (43.9)	1 (Ref)		
Arg/Gln + Gln/Gln	119 (60.7)	23 (56.1)	0.843	0.375–1.895	0.679
XRCC1 Arg194Trp					
Arg/Arg	173 (88.3)	36 (87.8)	1 (Ref)		
Arg/Trp + Trp/Trp	23 (11.7)	5 (12.2)	1.279	0.377–4.338	0.692
GSTP1 ILE105Val					
AA	95 (48.5)	13 (31.7)	1 (Ref)		
AG + GG	101 (51.5)	28 (68.3)	2.756	1.188–6.393	0.018
GSTA1 C-69T					
CC	59 (30.1)	8 (19.5)	1 (Ref)		
CT + TT	137 (69.9)	33 (80.5)	3.223	1.176–8.826	0.022
ENOS G894T					
GG	76 (38.8)	21 (51.2)	1 (Ref)		
GT + TT	120 (61.2)	20 (48.8)	0.478	0.215–1.065	0.071
TGFβ1 C-509T					
CC	85 (43.4)	18 (43.9)	1 (Ref)		
CT +TT	111 (56.6)	23 (56.1)	1.841	0.561–6.036	0.313
TGFβ1 T869C					
TT	71 (36.2)	19 (46.3)	1 (Ref)		
TC + CC	125 (63.8)	22 (53.7)	0.295	0.090–0.964	0.043
TP53 Arg72Pro					
Arg/Arg	110 (56.1)	29 (70.7)	1 (Ref)		
Arg/Pro + Pro/Pro	86 (43.9)	12 (29.3)	0.654	0.271–1.573	0.343

* Odds ratio adjusted for age, body mass index, breast diameter, follow-up, adjuvant treatment, history of vasculopathy, smoking status, dose per fraction, radiation quality, and boost method.


40
35
30
25
20
15
10
5
0
% of patients with G2-3 fibrosis
1/14
10/83
20/114
10/26
0
1
2
3
Number of concomitant genetic risk factors
(GSTP1 105Val, GSTA1 -69T, TGFß1 869TT)

Conclusions



-Our results suggest that functional variations in genes involved in oxidative stress response and fibroblast proliferation may modulate the development of radiation-induced fibrosis in breast cancer patients.

-Consisting but also equivicol results are reported in the literature.

-Unravelling the genetic basis of normal tissue complication risk will be more dif?cult and complicated than (probably) anticipated at ?rst.

-Standardized procedures for reporting clinical outcome data and dosimetric treatment parameters are needed.

-Future studies should probably be undertaken by consortia rather than single institutions.

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