The search for genetic predictors of radiotherapy response

Prof. Dirk De Ruysscher, MD, PhD
Radiation Oncologist
Maastro clinic
Maastricht
The Netherlands

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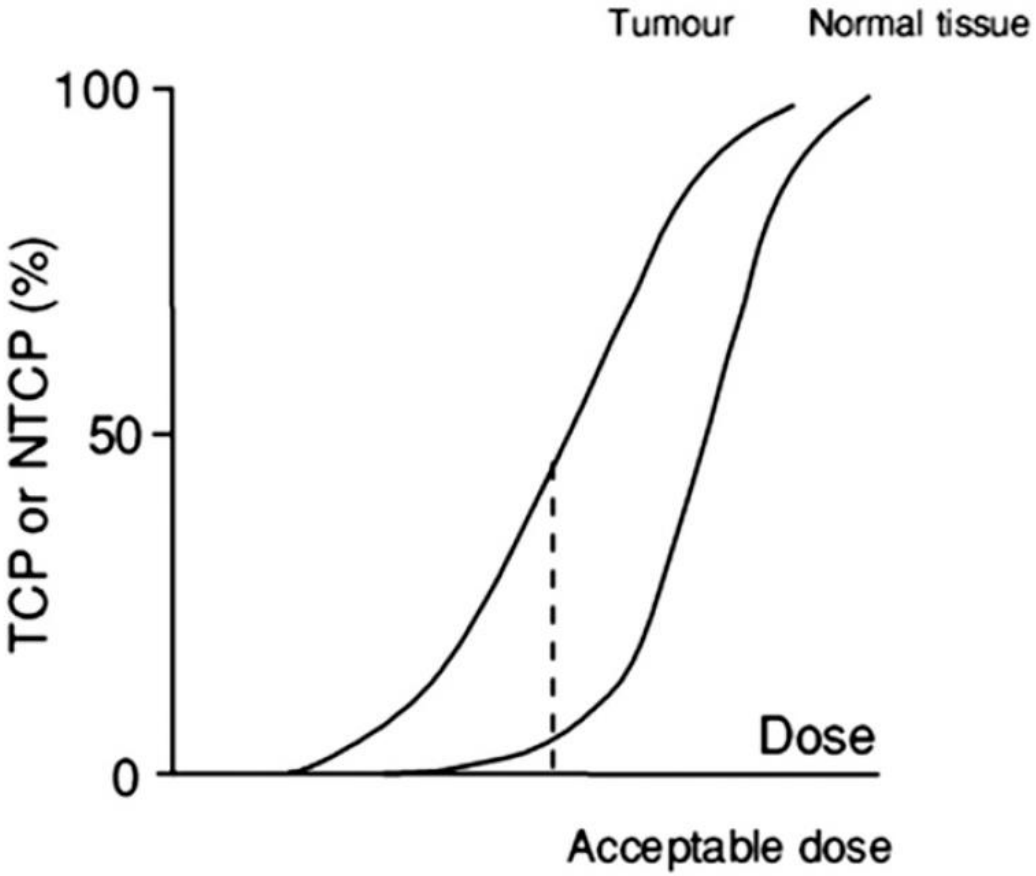
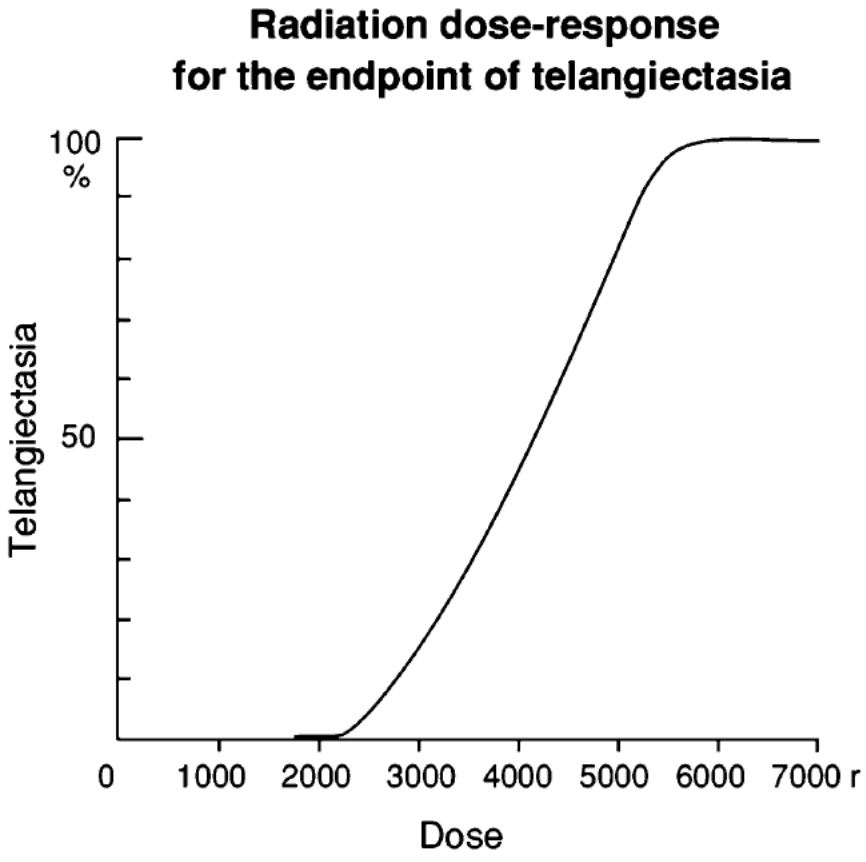
Why looking for predictors of normal tissue damage?



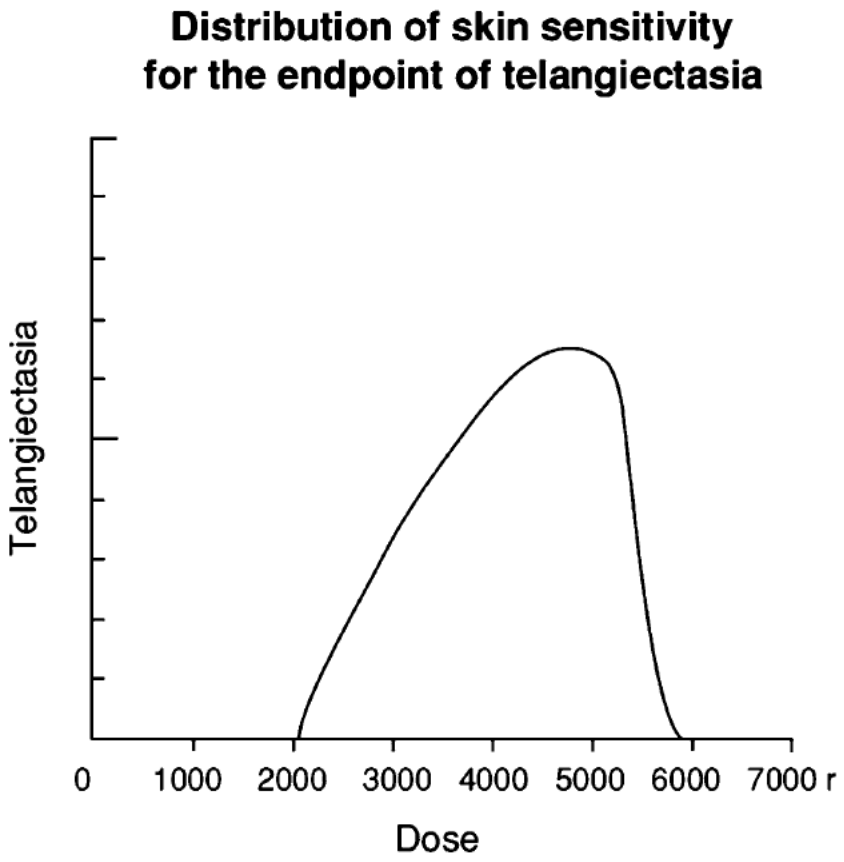
The 5 % most susceptible patients drive the "dose constraints"

Scaife et al. Br J Radiol 2015

Evidence for individual radiosensitivity



cumulative frequency distribution



differential frequency distribution

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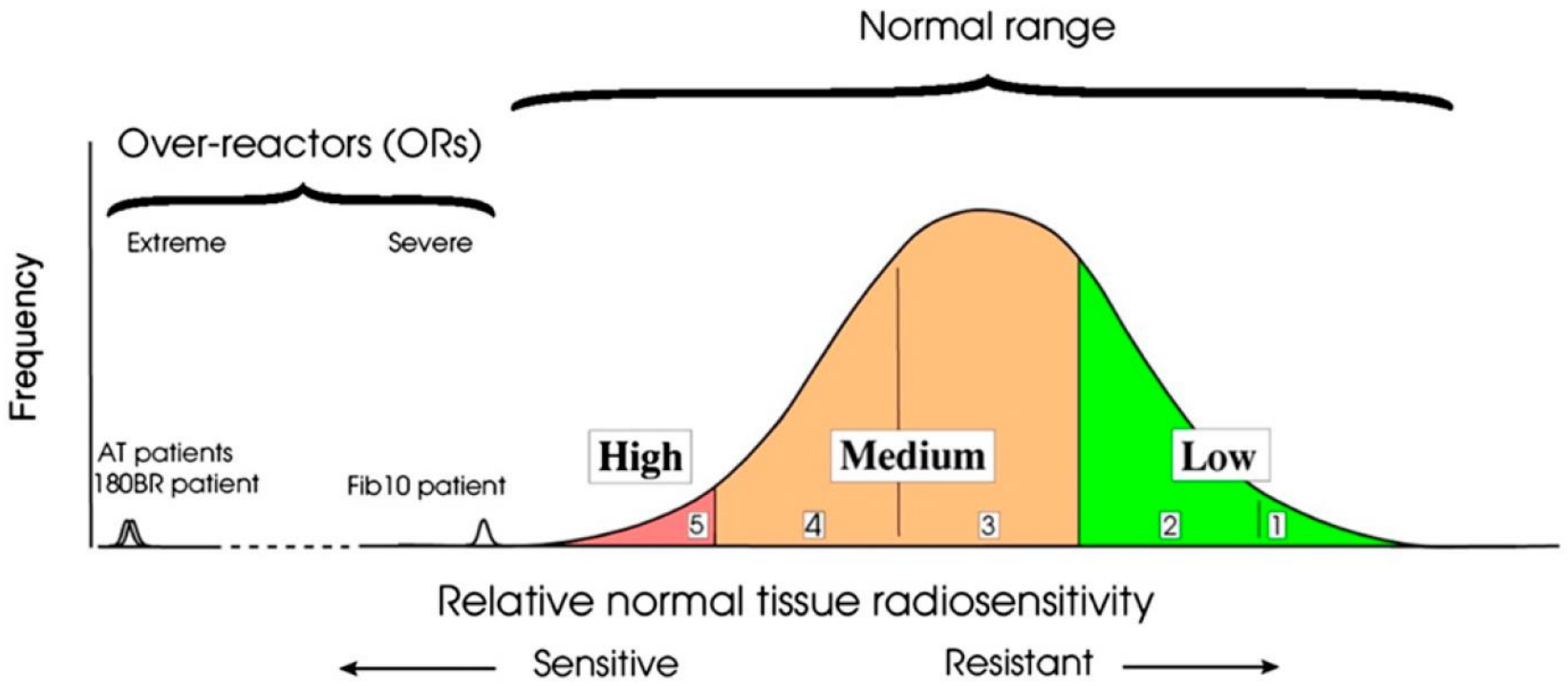
Individual radiosensitivity



Scaife et al. Br J Radiol 2015

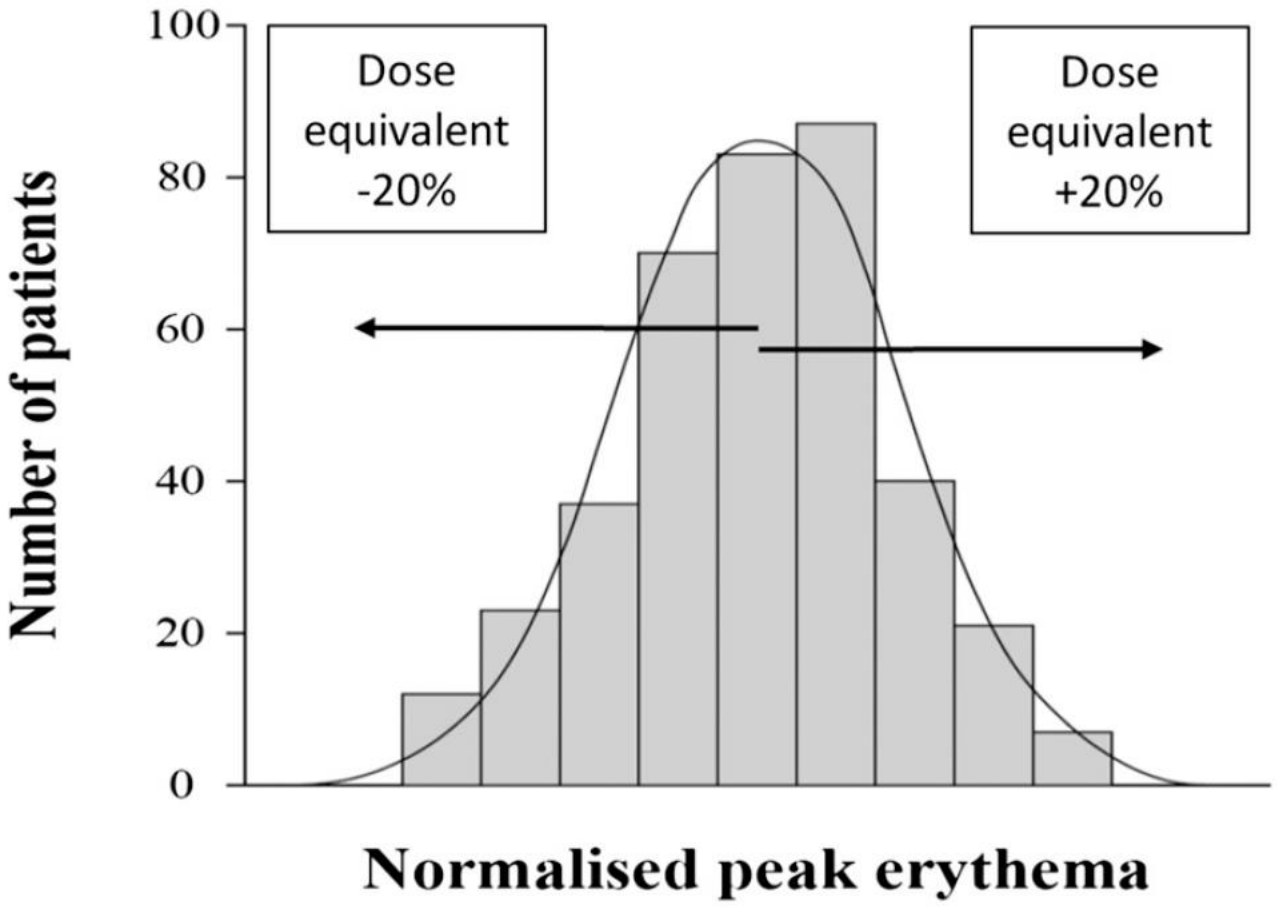
GENEPI: Over-reactors: *Very* rare

Details of the 11 over-reactor patients.

Age (years)	Gender (F: female; M: male)	Ethnicity	Cancer/systemic disease	Stage	Radiation total dose (Gy)/ No. fractions/overall treatment time (days)	Systemic treatment	Acute toxicity (<90 days post-radiotherapy)	Late toxicity (⩾90 days post-radiotherapy)
49	F	Caucasian	Non-small cell lung cancer	IV	30/10/14	Cisplatin-gemcitabine	Dysphagia G1 Skin G1	3 months: Fibrosis G4
64	F	Unknown	Breast cancer/ rheumatoid arthritis	"Localized"	45/20/32	5FU, epirubicin, cyclophosphamide, tamoxifen	Skin G1	173 days: Fibrosis G4
51	F	Unknown	Tongue	Unknown	60/30/57	None	Mucositis G4 necessitating a treatment break	572 days: Bilateral neuropathy optical tract
60	F	Caucasian	Atypical meningioma		59.4/33/55	None	None	88 days: Fibrosis G3
60	F	Caucasian	Breast cancer	I	66/33/45	None	Skin G3 after 15 Gy: completely resolved	3 years: Brachial plexopathy G3
70	F	Unknown	Breast cancer	RT0N3M0	45/20/26	None	Skin G1	596 days: Fibrosis G4
54	F	Unknown	Breast cancer	Unknown	55/25/33	Adriamycin, cyclophosphamide	Skin G2	381 days: Xerostomia G2, Dysphagia G2
72	M	Caucasian	Oropharyngeal cancer	IV	66/33/44	None	Mucositis G4 after 30 Gy	None
74	F	Asian	Breast cancer	IV	8/1/1	Letrozole	Skin G3	None
57	M	Unknown	Lymphoma	I	34/17/17	Cyclophosphamide, adriamycin, vincristine, prednisone	Skin G3 Pneumonitis G3	None
67	F	Unknown	Breast cancer	I	30/15/22	5FU, epirubicin, cyclophosphamide	Skin G3 after 30 Gy	None

De Ruysscher et al. Radiother Oncol 2010

Individual radiosensitivity



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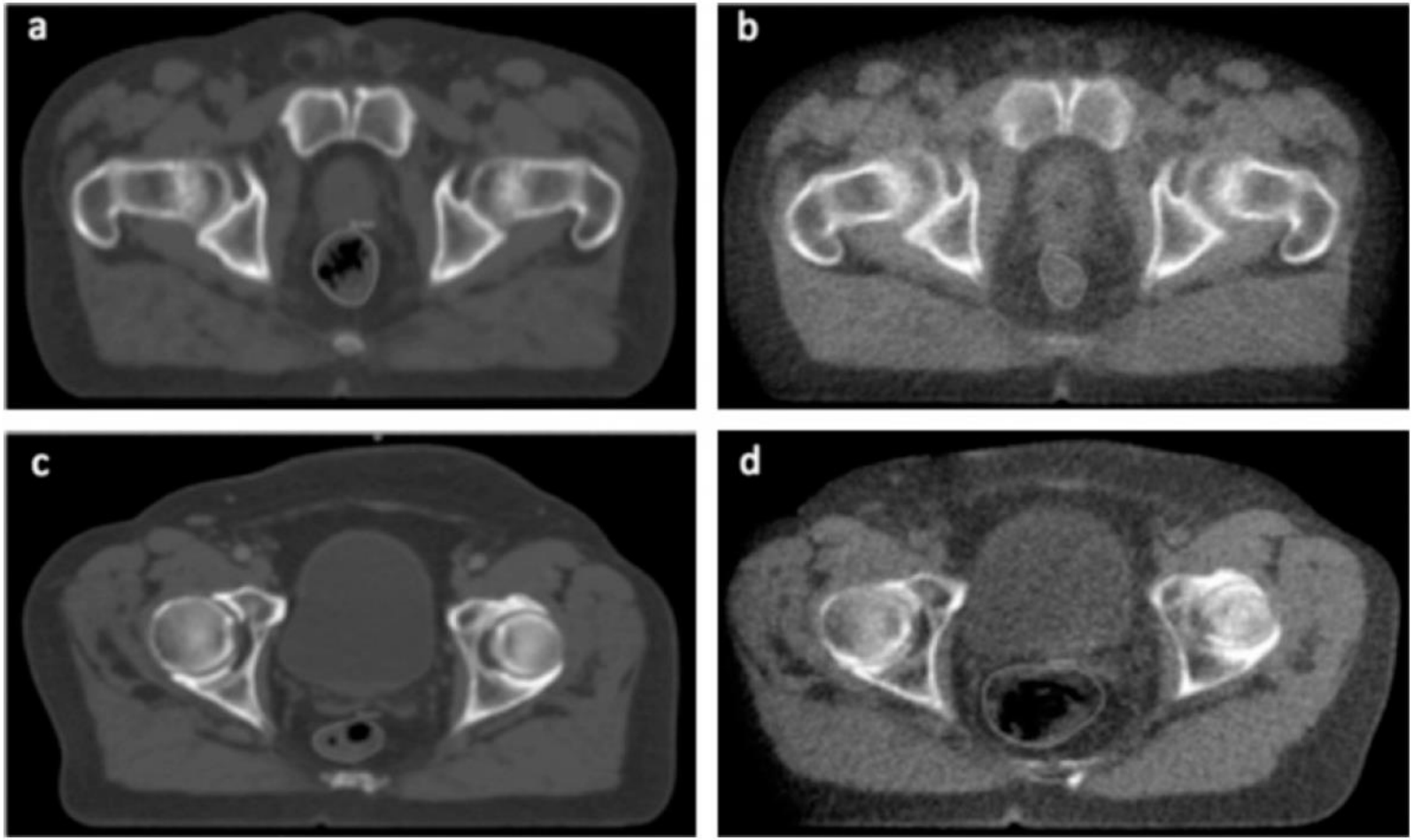
Caveat: Pseudo-individual radiosensitivity



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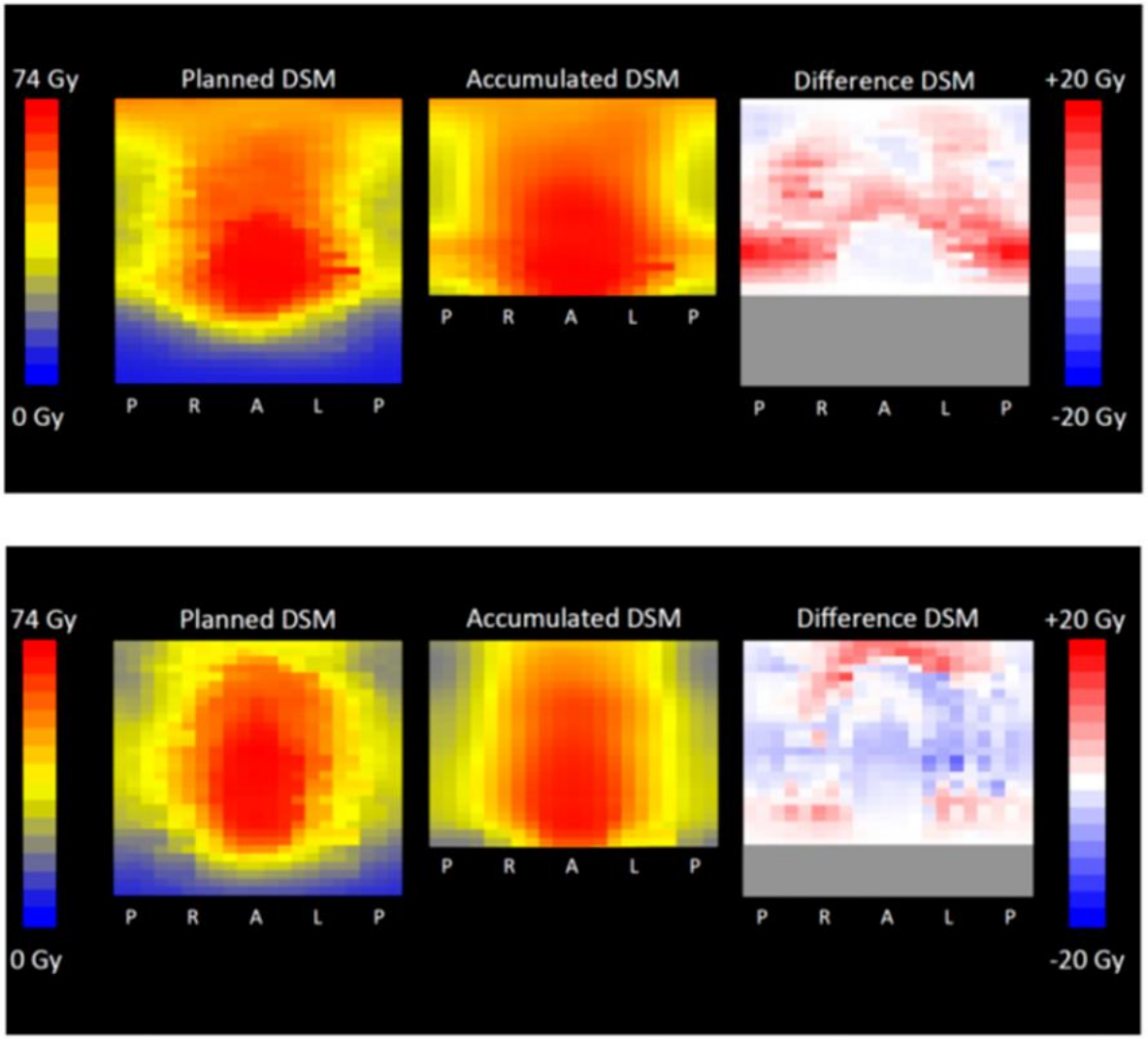


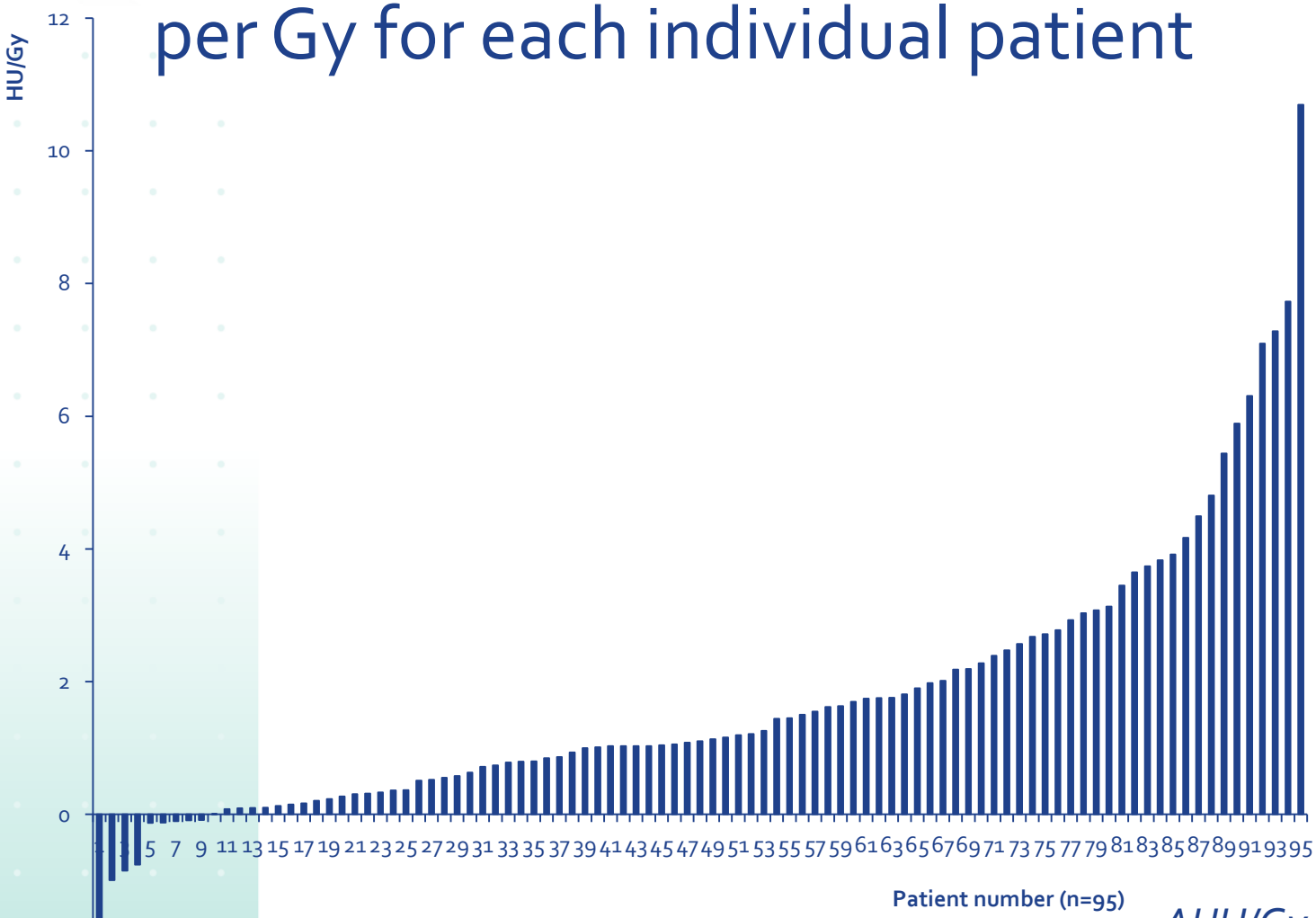
Scaife et al. Br J Radiol 2015

Review

STROGAR – STrengthening the Reporting Of Genetic Association studies in Radiogenomics

Sarah L. Kerns [a,b,c], Dirk de Ruysscher [d], Christian N. Andreassen [e], David Azria [f], Gillian C. Barnett [g], Jenny Chang-Claude [h], Susan Davidson [i], Joseph O. Deasy [j], Alison M. Dunning [k], Harry Ostrer [b,c], Barry S. Rosenstein [a], Catharine M.L. West [l], Søren M. Bentzen [m,*]

Imaging: Changes in Hounsfield Units (HU) per Gy for each individual patient



ΔHU/Gy and dyspnoea ≥ G2

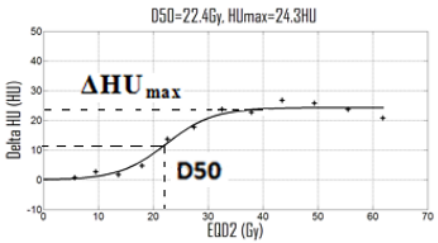
< median, 16/48 (33.3 %) > median, 17/47 (36.1 %) (p=0.77)

De Ruysscher et al. Acta Oncol 2013

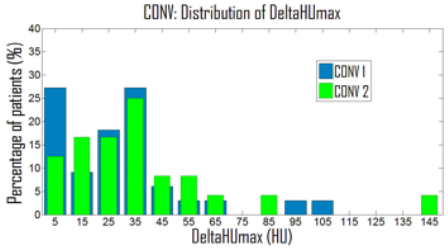
- The average timepoint of CT_{fup} was 2.3 months after end of radiotherapy.

- **Lung tissue damage description**: patient-specific dose response curves for density change were generated.
- Sigmoidal fits (with parameters ΔHU_{max} and D_{50}) outperformed linear fits.

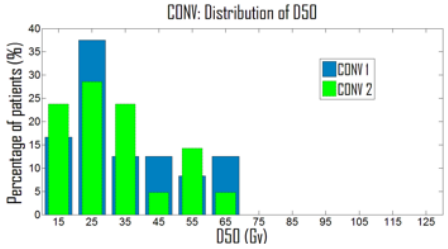
$HU_{fup} - HU_0$



for all patients



ΔHU_{max}



D_{50}

ΔHU_{max} : saturation level of the density change
D_{50} : dose at 50% of saturation

Defraene et al. Radiother Oncol 2015

Number of SNP needed for an AUC 0.75-0.95 in a low penetrance polygenic distribution

A. Using an SNP-Only Model

Incidence of late effects	AUC				
	0.75	0.80	0.85	0.90	0.95
30%	71 (60,80)	118 (100,226)	214 (196,228)	397 (382,418)	977 (928,1012)
5%	59 (52,64)	98 (92,104)	159 (150,168)	269 (248,282)	557 (520,580)

Kerns et al. Sem Radiat Oncol 2015

Number of SNP needed for an AUC 0.75-0.95 in a low penetrance polygenic distribution

B. Adding SNPs to an Existing NTCP Model

Incidence of late effects	NTCP model AUC	NTCP + SNP model AUC				
		0.75	0.80	0.85	0.90	0.95
30%	0.70	28 (22,36)	78 (72, 86)	171 (152, 180)	357 (325, 385)	928 (905, 970)
	0.75		49 (40,62)	145 (125, 164)	335 (310, 348)	868 (835, 900)
	0.80			75 (60, 90)	272 (256, 296)	821 (800, 855)
5%	0.70	24 (19, 28)	61 (52, 72)	118 (108, 126)	233 (224, 250)	529 (505-549)
	0.75		36 (29, 43)	96 (82, 106)	211 (200, 224)	501 (475, 525)
	0.80			53 (45, 61)	170 (165, 179)	460 (438, 478)

Kerns et al. Sem Radiat Oncol 2015

Replicated SNP associated with late radiation toxicity

SNP	MAF	Location	Nearest Gene(s)	Cancer Site	Toxicity End Point	Study Type
rs2868370	0.26	Promoter	HSPB1	Lung	Esophagitis	Candidate gene
				Lung	Pneumonitis	
rs1800469	0.31	Promoter	TGFB1	Lung	Esophagitis	Candidate gene
rs1800629	0.14	Promoter	TNF-α	Breast	Overall toxicity	Candidate gene
rs1139793	0.28	Exonic (missense)	TXNRD2	Breast	Fibrosis	Candidate gene
rs7120482	0.30	Intergenic	MTNR1B, SLC36A4	Prostate	Rectal bleeding	GWAS
rs264663	0.02	Intronic	TANC1	Prostate	Overall toxicity	GWAS

Kerns et al. Sem Radiat Oncol 2015

Confirmed SNP-associated RT toxicity

Confirmed SNP (Gene)	Toxicity Endpoint	Cancer site	Sample Size	Study Type	Discovery set ES (95% CI)	Discovery set p-value	Replication set I ES (95% CI)	Replication set I p-value	Replication set II ES (95% CI)	Replication set II p-value
rs2868371 (CG/GG vs CC) (HSPB1)	Esophagitis (grade ≥ 3 vs. grade ≤ 2)	Lung	301 (120 discovery set, 181 replication set)	Candidate	HR=0.29† (0.09,0.97)	0.045	HR=0.25† (0.07,0.88)	0.031	NA	NA
rs1800469 (CT/TT vs CC) (TGFB1)	Esophagitis (grade ≥ 3 vs. grade ≤ 2)	Lung	198 (97 discovery set, 101 replication set)	Candidate	HR=2.47† (1.02,6.02)	0.045	HR=2.53† (1.14,5.63)	0.023	NA	NA
rs1800629 (AA vs AG/GG) (TNF-α)	Overall toxicity (quantitative variable)	Breast	3,036 (340 discovery set, 748 replication set I, 948 replication set II)	Candidate	OR=2.6†* (0.9,7.1)	0.0028	OR=4.0†* (1.5,10.8)	0.04	OR=2.0 (1.0,3.9)	0.01 (rs2857595)
rs2868371 (CG/GG vs CC) (HSPB1)	Pneumonitis (grade ≥ 3 vs. grade ≤ 2)	Lung	271 (146 discovery set, 125 replication set)	Candidate	NA	0.031	NA	0.025	NA	NA
rs1139793 (TXNRD2)	Fibrosis (grade ≥ 3 vs. grade ≤ 2)	Breast	375 (92 discovery set, 283 replication set)	Candidate	OR=2.38† (0.82,6.84)	0.0205	OR=7.53† (2.08,27.2)	0.007	NA	NA
rs7120482 (intergenic)	Rectal bleeding (grade ≥ 2 vs. grade ≤ 1)	Prostate	1,149 (368 discovery set, 781 replication set)	GWAS	OR=6.7† (2.8,16.1)	2.4×10^{-5}	OR=3.1† (1.7,5.6)	2.1×10^{-4}	NA	NA
rs264663 (TANC1)	Overall toxicity (quantitative variable)	Prostate	1,266 (417 discovery set, 579 replication set I, 270 replication set II)	GWAS	OR=6.6†* (2.2,19.6)	4.09×10^{-9}	OR=6.9†* (2.5-19.3)	1.15×10^{-4} (rs7582141)	NA	0.031 (rs7582141)

Kerns et al. Future Oncol 2014

Conclusions

- There is definitely a genetic base for some of the observed individual differences in radiosensitivity
- The genetics now have matured
- Accurate reporting is needed
- Combination of genetic information with NTCP (multi-factorial) models and imaging improves the model and decreases the number of patients needed
- Be aware of technical issues such as the real dose delivered that may lead to erroneous conclusions