Genetic pathways for the prediction of the effects of ionising radiation

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GENEPI-lowRT

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EURATOM

CANCER RESEARCH UK

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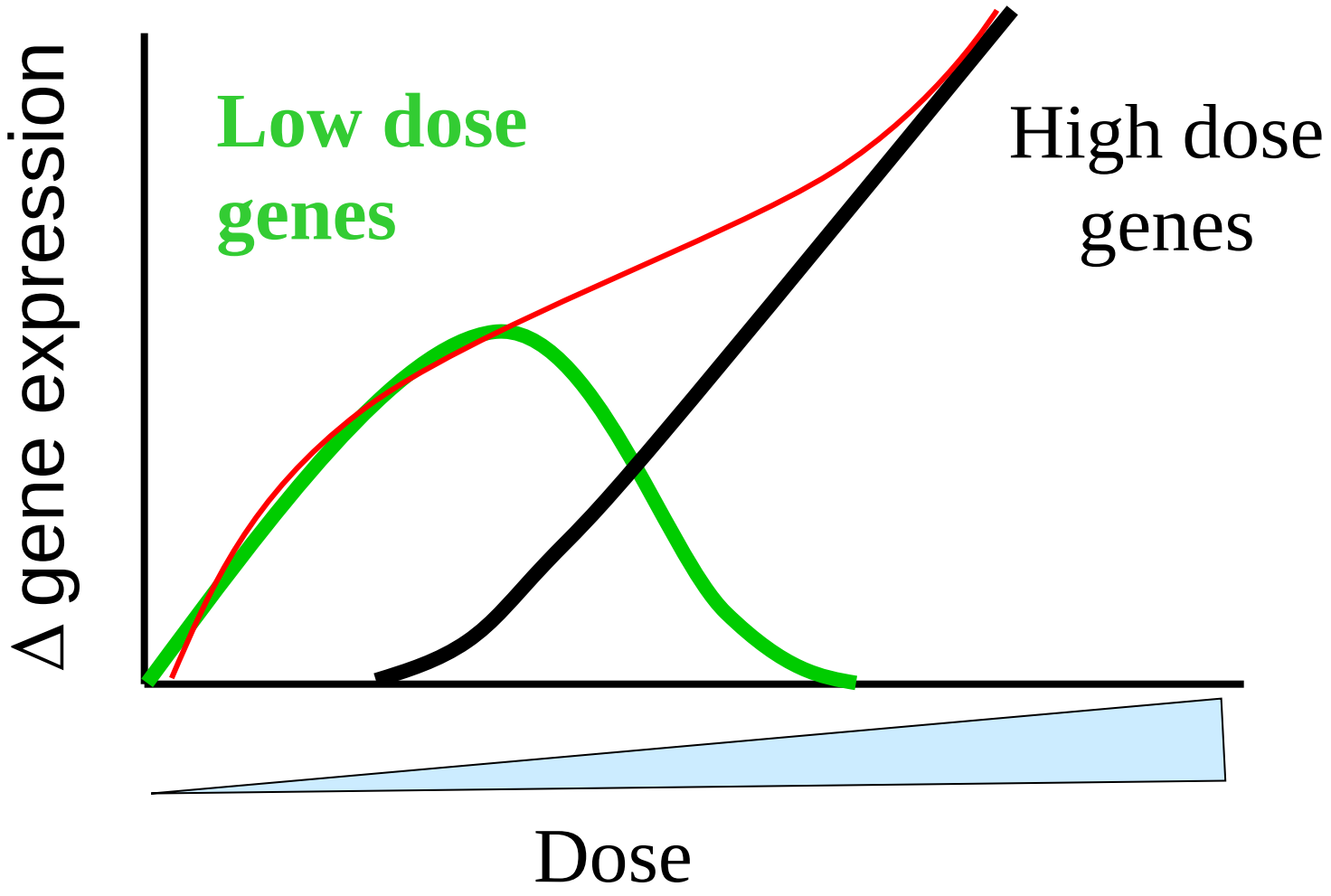
Aim of GENEPI-lowRT project

To test for associations between:-

- the risk of severe normal tissue toxicity following curative radiotherapy for early breast cancer
- *in vitro* transcriptional and cellular responses induced in lymphocytes and dermal fibroblasts by low dose ionising radiation.

Identify any links between radiosensitivity and genetic differences of individuals

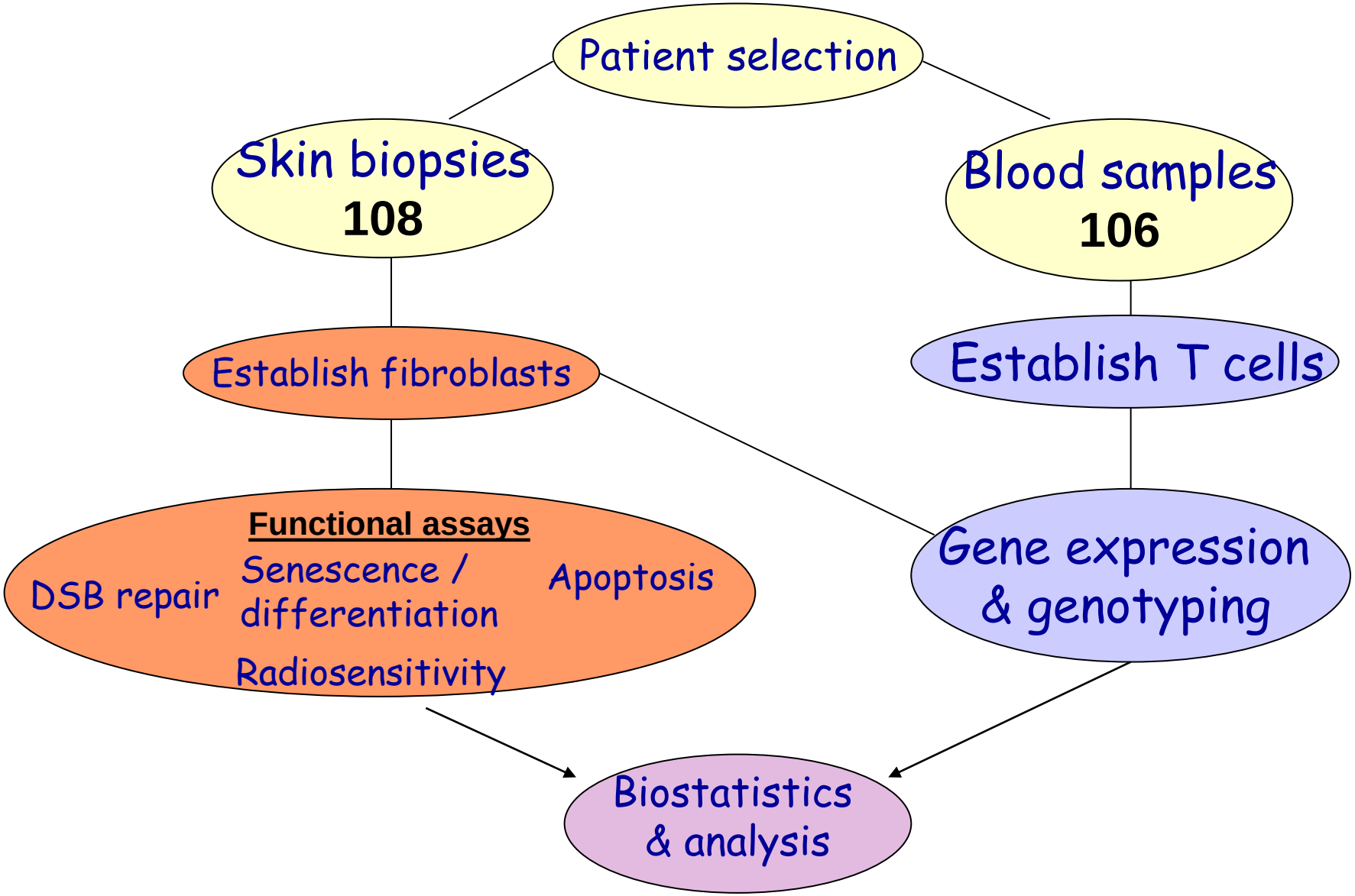
Radiation-induced changes in gene expression



Background

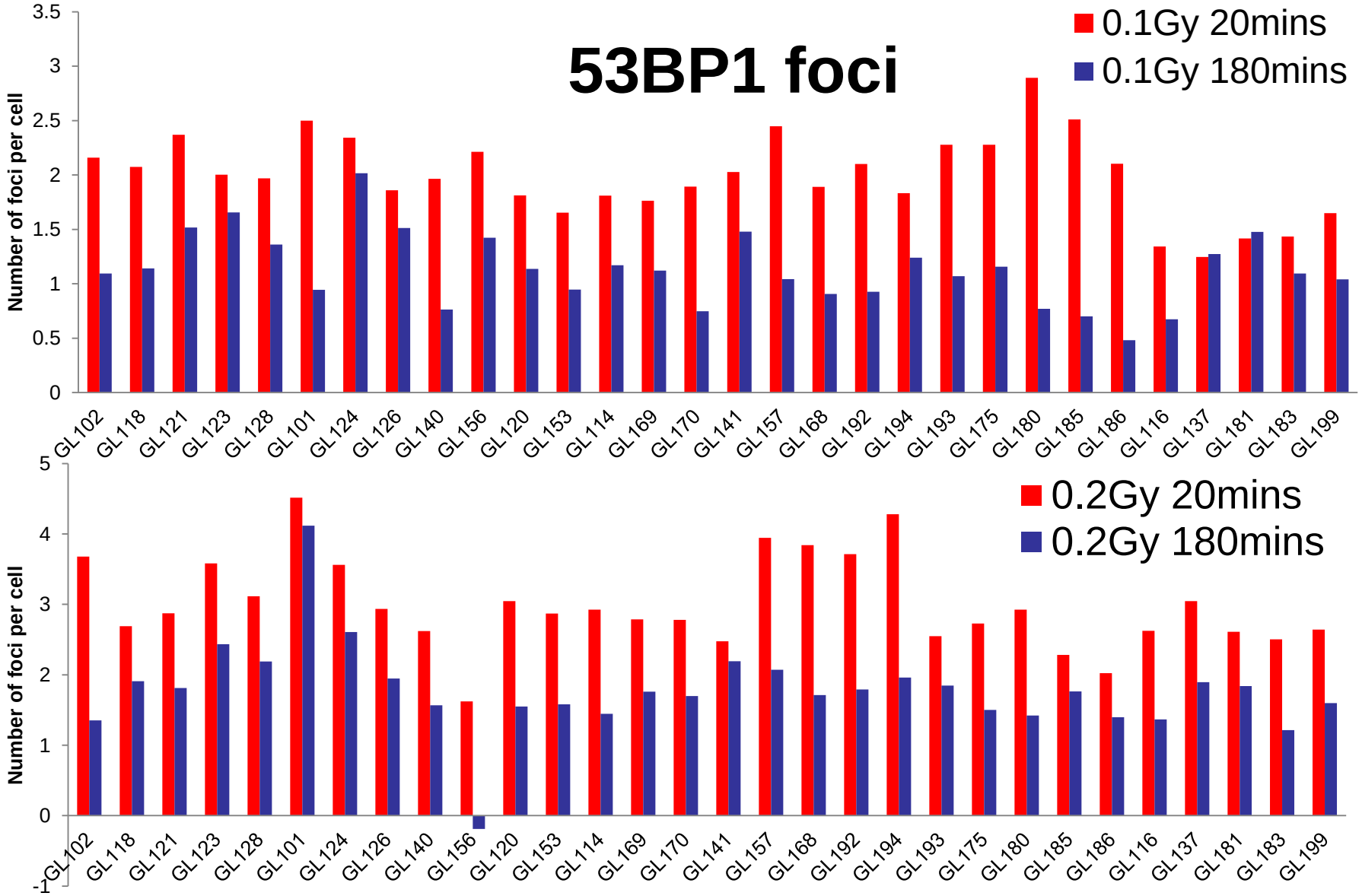
Predictive studies at high dose (≥2Gy) have not been particularly successful on heterozygotes.

Schematic of approach



Similar numbers of normal relative to over responders

Change in DNA damage marker response in **radiosensitive** patients at 0.1 and 0.2 Gy

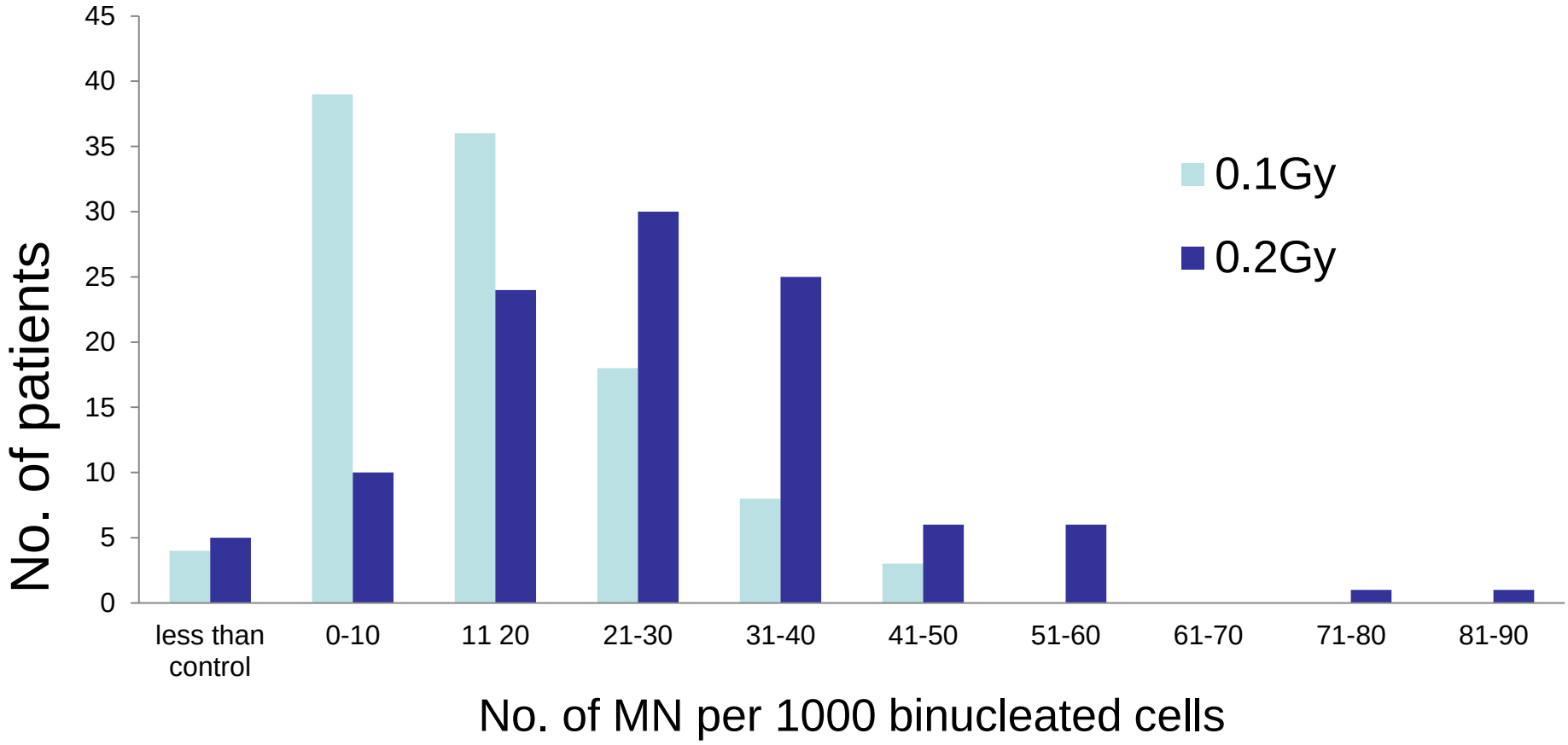


Percentage repair in normal and radiosensitive patient cohorts at 0.1 and 0.2Gy

Percentage of repair	normal	RS	normal	RS
	0.1 Gy		0.2 Gy	
0-10	3	6	4	3
11-20	8	11	5	8
21-30	9	8	9	11
31-40	7	4	9	7
41-50		1	3	1
51-60	3			

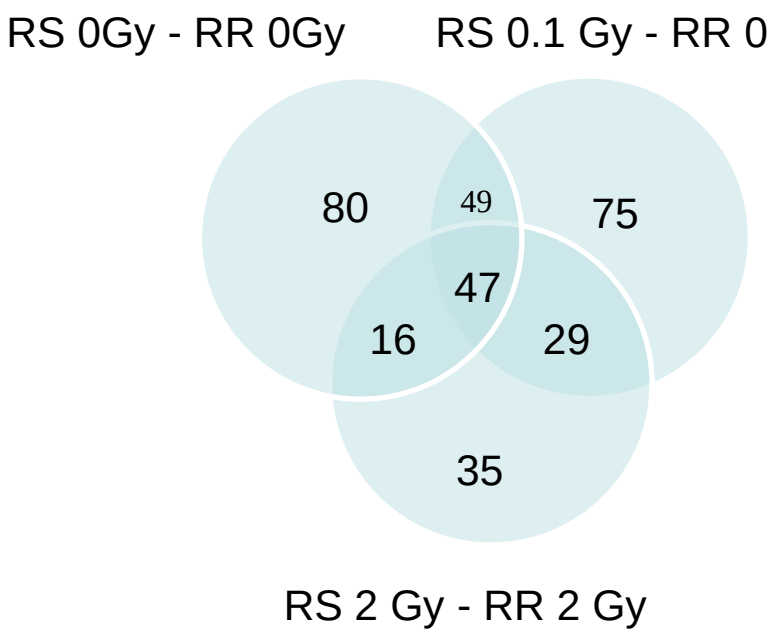
No predictive power for radiosensitive cohort

Chromosomal radiosensitivity of patient fibroblasts measured by the micronuclei assay

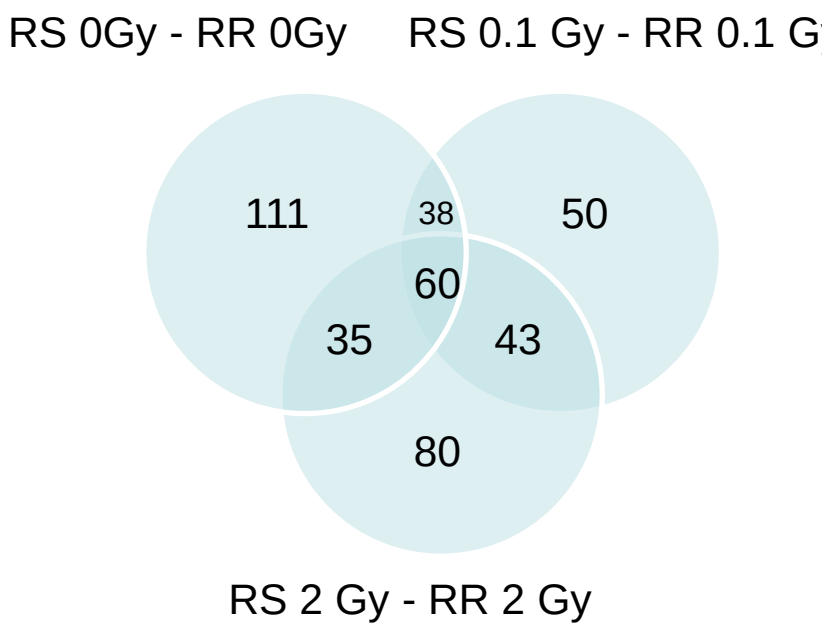


No predictive power for radiosensitive cohort

Differential gene expression at different doses



up **22404**



down **22318**

4 genes up-regulated at 0.1 Gy relative to 2 Gy

genes related to age at menopause
gene that interacts with BRAC2

High dose - *cell cycle regulation , DNA repair and DNA replication*

Gene sets from 2 Gy data with lymphocytes- Bioinformatic analysis

EntrezID	Gene Symbol	GeneName
729595	HMGB3P22	high-mobility group box 3 pseudogene 22
7516	XRCC2	X-ray repair complementing defective repair in Chinese hamster cells 2
6503	SLA	Src-like-adaptor

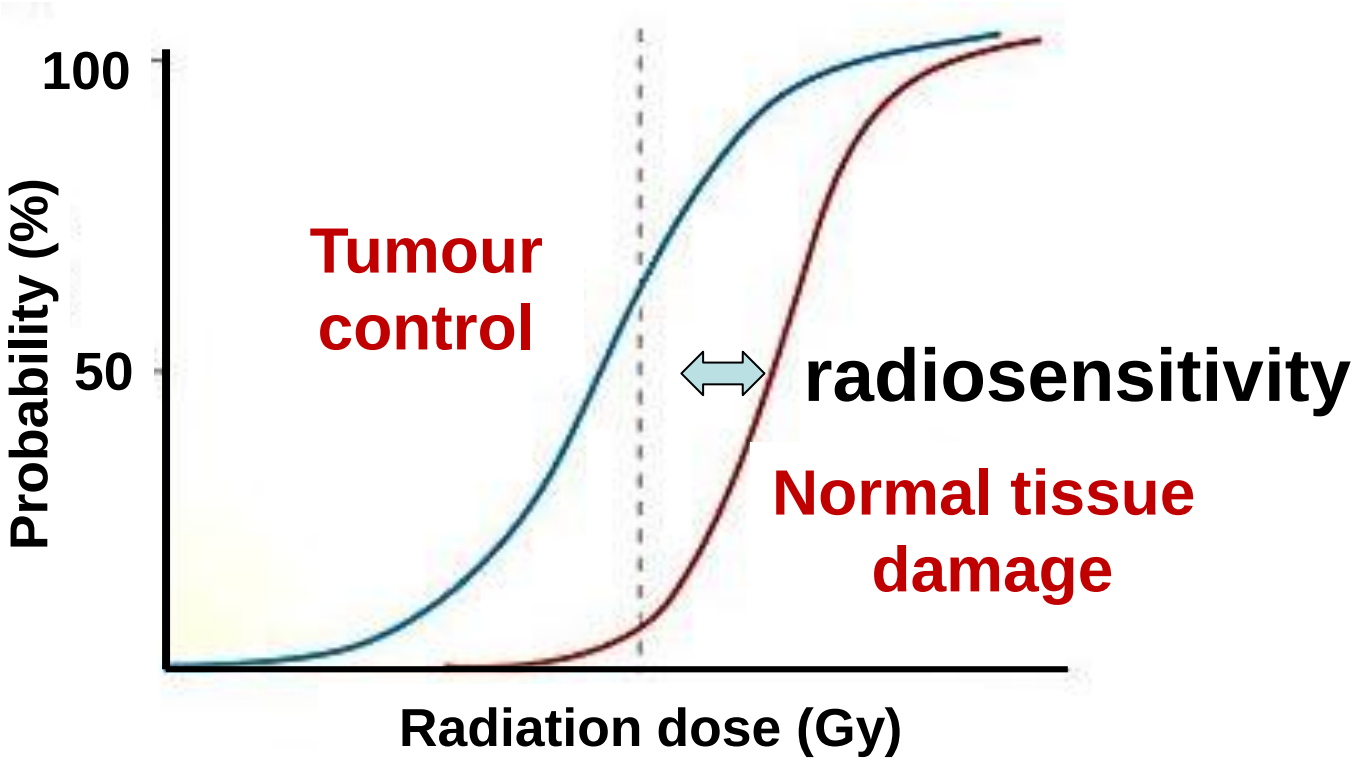
Bioinformatic analysis still ongoing

Summary

A robust classifier for radiosensitivity to late effects of radiation could not as yet be established at high or low dose.

Unidentified confounding factors may contribute to the radiosensitivity

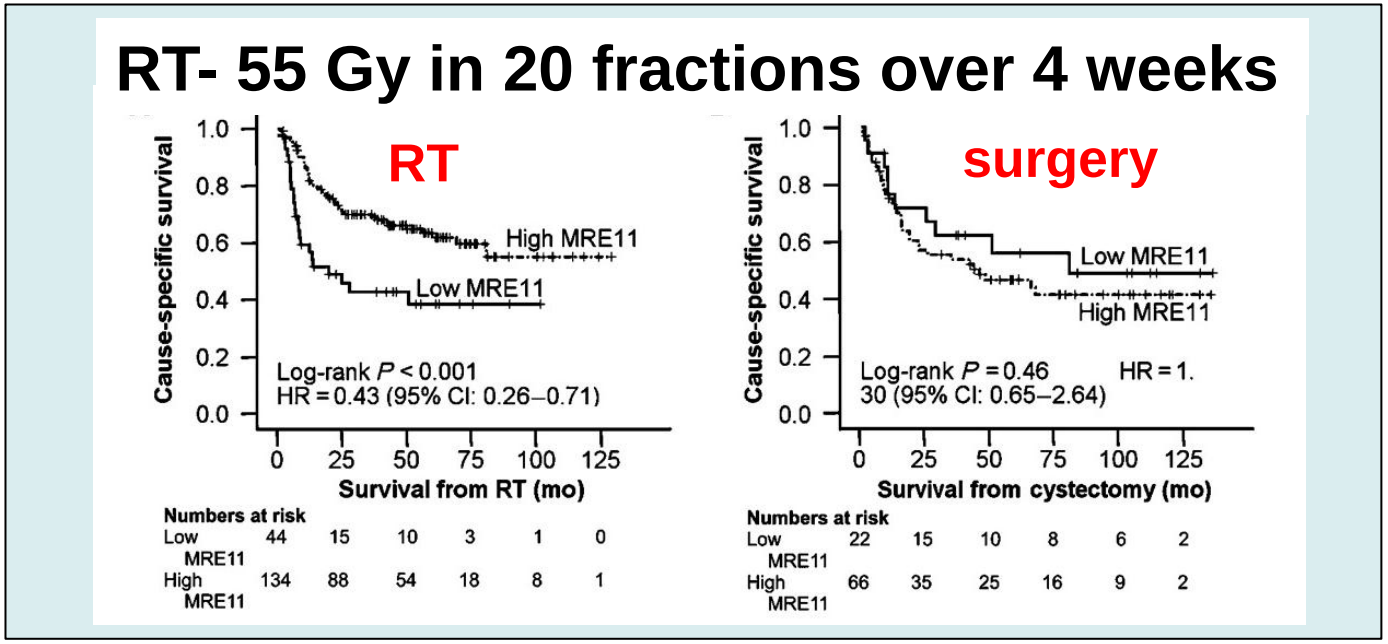
Dose response curve for radiotherapy



The effectiveness of radiotherapy limited by radiation doses needed to minimise normal tissue damage

MRE11 predictive factor in radical radiotherapy

Radical radiotherapy and surgery achieve similar cure rates in muscle-invasive bladder cancer.
Choice of which treatment is most beneficial cannot be predicted for individual patients.



MRE11 protein expression

predictive factor associated with survival following bladder cancer RT

NOT **a prognostic marker** in bladder cancer.

Allows patient selection for radiotherapy or cystectomy

Kiltie *et al* Cancer Res; 70(18); 7017–26 (2010)

Single nucleotide polymorphisms

correlation with clinical radiosensitivity-

Mismatch repair mechanisms –MSH2 and MSH3

Int. J. Radiation Oncol. Biol. Phys. 81, 52 (2011)

No association between SNPs regulating TGF-beta 1 secretion and late radiotherapy toxicity to the breast: results from the RAPPER study

Barnett et al, Radiother. Oncol. 97 SI, 9(2010)

Global gene expression responses to low and high dose radiation different in 3D tissue models

- Low dose recovery and tissue repair
- High dose loss of structural integrity and terminal differentiation

Amundson et al, Radiat Res. 175, 677 (2011)

Future research

Established the extent to which individual sensitivity is dependent on :-

- **genetic background in contrast to the role played by potentially modifiable lifestyle factors**
- **inflammatory and immunological factors**

Genetic approaches

Use well-defined cohorts to define the role individual radiosensitivity to low and high dose radiation and latencies for different pathologies (cancer, non-cancer diseases).

Based on knowledge on gene expression and genetic polymorphisms In DNA repair, cell cycle checkpoint, oncogenes, metabolism, hormonal and immune responses etc. **BIOMARKERS**

AND

Identification of epigenetic effects

Future research

For the detection of individual sensitivity

set up suitable (dosimetrical and medical) cohorts that are well controlled together with appropriate infrastructures

Biodosimetry

Genomic and proteomic modulation induced by ionising radiation

Both studies identified

cycline dependent kinase inhibitor (CDKN1A)
apoptotic gene (BBC3)
DNA damage inducible protein 45 α gene (GADD45A)

Turtoi et al, Int. J. Radiat. Biol. 86, 888 (2010)
Badie *et al* Int. J. Radiat. Biol. 87, 115 (2011)

Policy impact

From a radiation protection point of view

and risk stratification of patients for Radiotherapy

it is important to identify radiation sensitive individuals and to understand the mechanisms involved.

Diagnostic radiology including CT scans – hypersensitivity to ionising radiation (including infants and children and pregnant women)

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