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Single Nucleotid Polymorphisms of XRCC1, XRCC3, RAD51 and associated haplotypes predict for acute toxicity in patients with locally advanced rectal cancer treated with preoperative radiochemotherapy.

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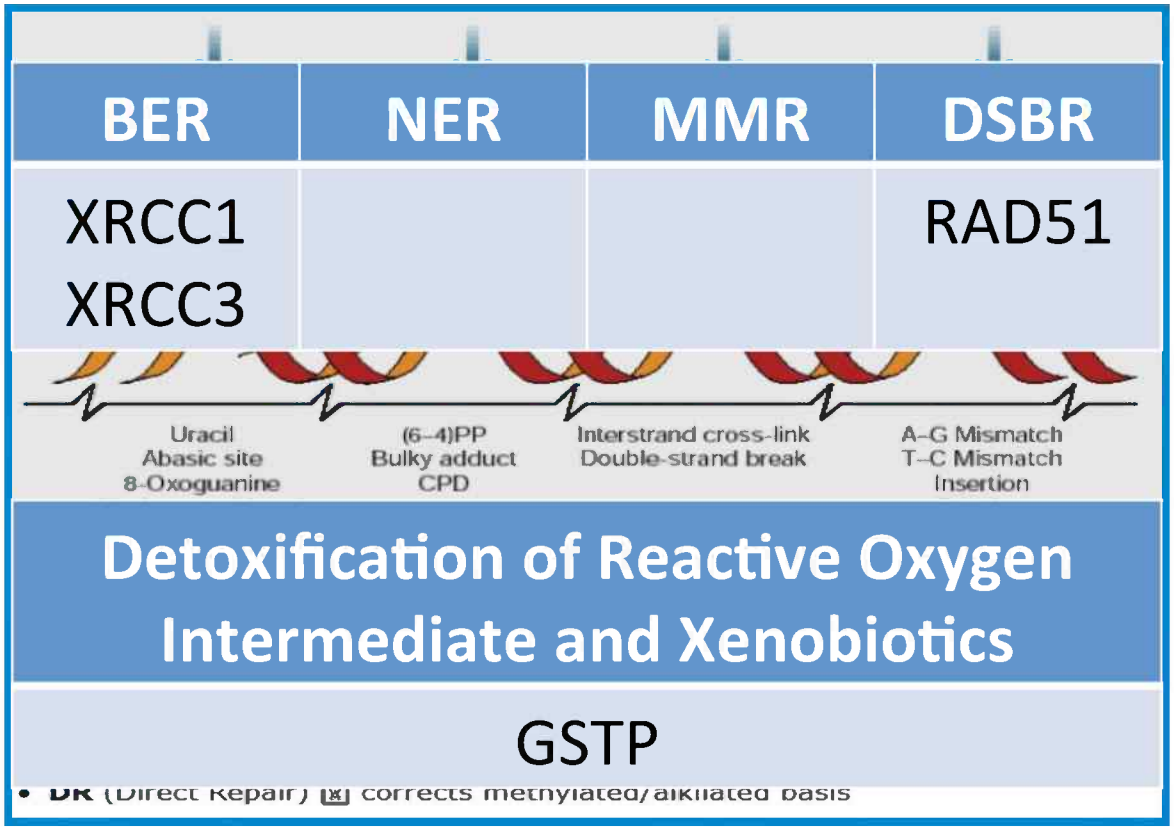
Background

Ionizing radiations act through DNA damage



Altered function of those mechanism can lead to low repair ability → more damage

Background

- XRCC1 (G28152A) encode for a protein with low repair activity. Higher incidence of acute and late toxicities in prostate, nasopharingeal and rectal cancer

Vodicka P., et al. Carcinogenesis 2004. Haijun Li , et al. Rad Onc. 2013. Balboa E, et al. Pharmacogenomics 2010. Langsenlehner T, et al. Radiother Oncol. 2011

- RAD51 (G315C) may lead to a m-RNA and a consequent low protein expression. High toxicity in prostate cancer patients.

Russell J.S., et al. Cancer Res. 2003. Levy-Lahad E., et al. ProcNatlAcadSciU.s.A. 2001. Van Oorschot B., et al. IntJRadiatOncolBiol Phys. 2014

Background

- XRCC3 (A4541G) encode for a protein with low repair activity. High rectum and bladder toxicity in prostate and bladder cancer patients.

Damaraju S., et al. ClinCancer-Res. 2006. Fachal L., et al. RadiotherOncol. 2012. Sakano S., et al. Pharmacogenomics. 2010

- XRCC3 (C18067T) encode for a protein with low repair activity. High *in vitro* radiosensitivity

Alsbeith G., et al. IntjRadiatOncolPhys. 2007

Background

- GSTP1 (A313G) therefore a reduced catalytic activity due to an altered affinity with the electrophile substrate

Ambrosone c. B., et al. Breast Cancer Res. 2006

SNPs of XRCC1, XPD, and TP53 may predict acute toxicity in a population of 132 locally advanced rectal cancer patients treated with Neoadjuvant Radiochemotharapy (N-RCT)

Duldulao, et al. Cancer 2013

Rationale

Grade≥3 adverse effects can lead to discontinuity of treatments that can reduce the outcome and may require hospitalitazion with increase in resources spent on patients

In some studies it is reported a rate of acute severe toxicity, after N-RCT with fluoropyrimidine in a range from 1% to 15%.

Hofheinz RD, et al. Lancet Oncol 2012

End-point

Series of 67 patients (locally advanced rectal cancer) treated with N-RCT

Primary end-point: high-grade acute toxicities during N-RCT can be predicted by Single Nucleotid Polymorphisms (SNPs):

XRCC1 G28152A
XRCC3 A4541G
XRCC3 C18067T
RAD51 G315C
GSTP1 A313G

Secondary end-point: high-grade acute toxicities during N-RCT can be predicted by combinations of SNPs

Materials and Methods

Patients' characteristics and clinical outcome (n=67).

	No. pts (% of tot)
Mean age (years)	64
Range (years)	36-85
Gender	
- Male	38 (57)
- Female	29 (43)
T, stage	
- T2	7 (10)
- T3	56 (84)
- T4	4 (6)
N, stage	
- N0	31 (46.5)
- N1	29 (43.5)
- N2	7 (10)
Distance from anal verge	
- ≤ 5cm	36 (54)
- > 5cm	31 (46)
Longitudinal extension	
- ≤ 5cm	30 (45)
- > 5cm	37 (55)
Surgery procedure	
- AR	56 (83.5)
- APR	9 (13.5)
- TAE	1 (1.5)
- No surgery	1 (1.5)

Locally advanced rectal cancer patients

Stage II-III

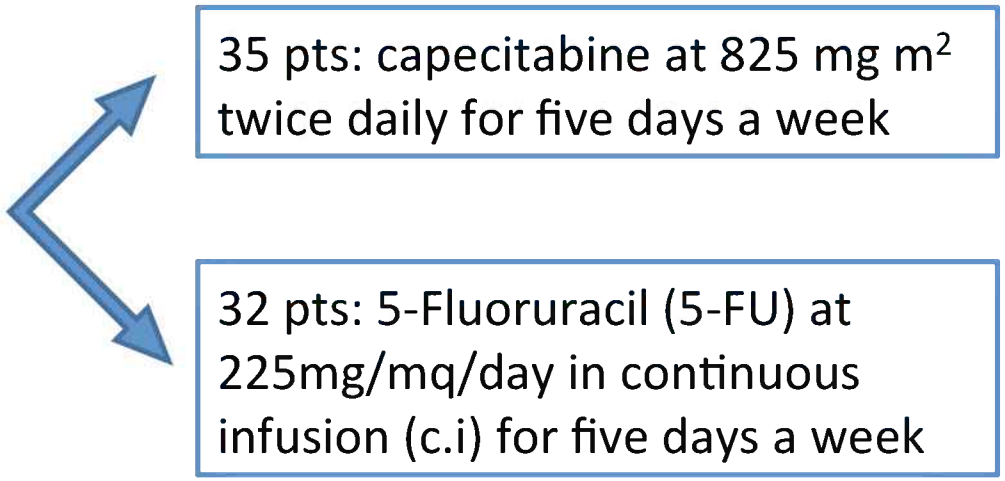
Blood samples for the study of SNPs

(*Pyrosequencing technology*)

Materials and Methods

Neoadjuvant Treatment

3DRT: 1,8Gy in 25 fr (total dose 45 Gy) + concomitant boost on GTV twice weekly, 1 Gy in 10 fr (total dose on GTV 55 Gy)



66 of 67 patients underwent surgical resection 8 weeks after N-RCT

Materials and Methods

Acute toxicities were scored, according to the CTCAE v3.0, in terms of:

Organ-non-specific acute toxicity (gastro-intestinal, hematological, skin and genitourinary)

Organ-specific acute toxicity (diarrhea, abdominal/pelvis pain**,** rectal discomfort, rectal bleeding, nausea/vomiting, proctitis, haemoglobin, leukocytes, platelets, cistitis, hematuria**,** urinary frequency/urgency).

Acute toxicity was considered as severe for grade ≥ 3, and when quality of life was significantly impaired.

Trotti A., SeminRadiatOncol 2003

Materials and Methods

Patients were classified into three groups for each gene:

- normal homozygous group (NH; patients who doesn't carry the SNP),
- heterozygous group (H; patients heterozygous for the SNP) and mutated
- homozygous group (MH; patients homozygous for the SNP).

NH vs. H
NH vs. MH
NH vs. H+MH

overall acute toxicity
organ-non-specific acute toxicity
organ-specific acute toxicity

Materials and Methods

Polymorphisms characteristics.

Allelic assessment	Polymorphisms				
	XRCC1 G28152A (n=67)	XRCC3 A4541G (n=67)	XRCC3 C18067T (n=67)	RAD51 G315C (n=67)	GSTP1 A313G (n=66)
NH	26 (39)	40 (60)	31 (46.5)	58 (86.5)	38 (57.5)
H	31 (46)	24 (35)	25 (37)	8 (12)	21 (32)
MH	10 (15)	3 (5)	11 (16.5)	1 (1.5)	7 (10.5)

NH: Normal Homozygous; H: Heterozygous; MH: Mutated Homozygous.

Results - Toxicities

Acute toxicity rates based on NCI CTCAE v. 3.0

Toxicity	*Grade 1-2*		*Grade 3-4*		*Total*	
	N.	%	N.	%	N.	%
Gastrointestinal						
Diarrhea	28	(42)	2	(3)	31	(45)
Abdominal/pelvis	6	(9)	4	(6)	10	(15)
pain	16	(24)	6	(9)	22	(33)
Rectal discomfort	5	(7.5)	1	(1.5)	6	(9)
Rectal bleeding	4	(6)	1	(1.5)	5	(7.5)
Nausea/vomiting	21	(31)	0	(0)	21	(31)
Proctitis	16	(24)	1	(1.5)	17	(25)
Skin erythema						
Haematological						
Hemoglobin	6	(9)	2	(3)	7	(12)
Platelets	5	(7.5)	0	(0)	5	(7.5)
Leukocytes	12	(18)	1	(1.5)	13	(19.5)
Genitourinary						
Cystitis	12	(18)	9	(13.5)	21	(31.5)
Hematuria	3	(4.5)	1	(1.5)	4	(6)
Urinary frequency/urgency	5	(7.5)	3	(4.5)	8	(12)

Results – Single SNPs analysis

Alleles correlations	*XRCC1 G28152A*			*XRCC3 A4541G*			*RAD51 G315C*		
	NH vs H+MH	*NH vs H*	*NH vs MH*	*NH vs H+MH*	*NH vs H*	*NH vs MH*	*NH vs H+MH*	*NH vs H*	*NH vs MH*
Gastroinstestinal (Grade ≥ 3)	0.717	0.619	0.895	0.785	1.0	0.487	0.06	0.036	0.734
Abdominal/pelvis pain	0.559	0.661	0.470	0.520	0.594	0.570	0.027	0.017	0.850
Skin erythema (Grade ≥ 3)	0.422		0.102	0.408	0.435	0.749	0.691	0.708	0.895
Skin erythema (any Grade)	0.03	0.044	0.061	0.1	0.194	0.015	0.04	0.101	0.074
Urinary frequency/urgency	0.311	0.452	0.367	0.031	0.022	0.001	0.485	0.510	0.815

NH: Normal Homozygous; H: Heterozygous; MH: Mutated Homozygous.

Results – Combined analysis

Univariate analysis for combined polymorphisms (haplotypes) (*p* values).

Alleles correlations	*RAD51 G315C + XRCC1 G28152A (n=24)* both NH vs both mutated	*XRCC1 G28152A + XRCC3 A4541G (n=27)* both NH vs both mutated	*RAD51 G315C + XRCC3 A4541G (n=39)* both NH vs both mutated	*RAD51 G315C + XRCC1 G28152A + XRCC3 A4541G (n=13)* NH vs mutated
Abdominal/pelvis pain	0.002		0.732	
Skin erythema (G3-4)			0.732	
Skin erythema (any G)	0.003	0.01	0.017	0.000

NH: Normal Homozygous; H: Heterozygous; MH: Mutated Heterozygous.

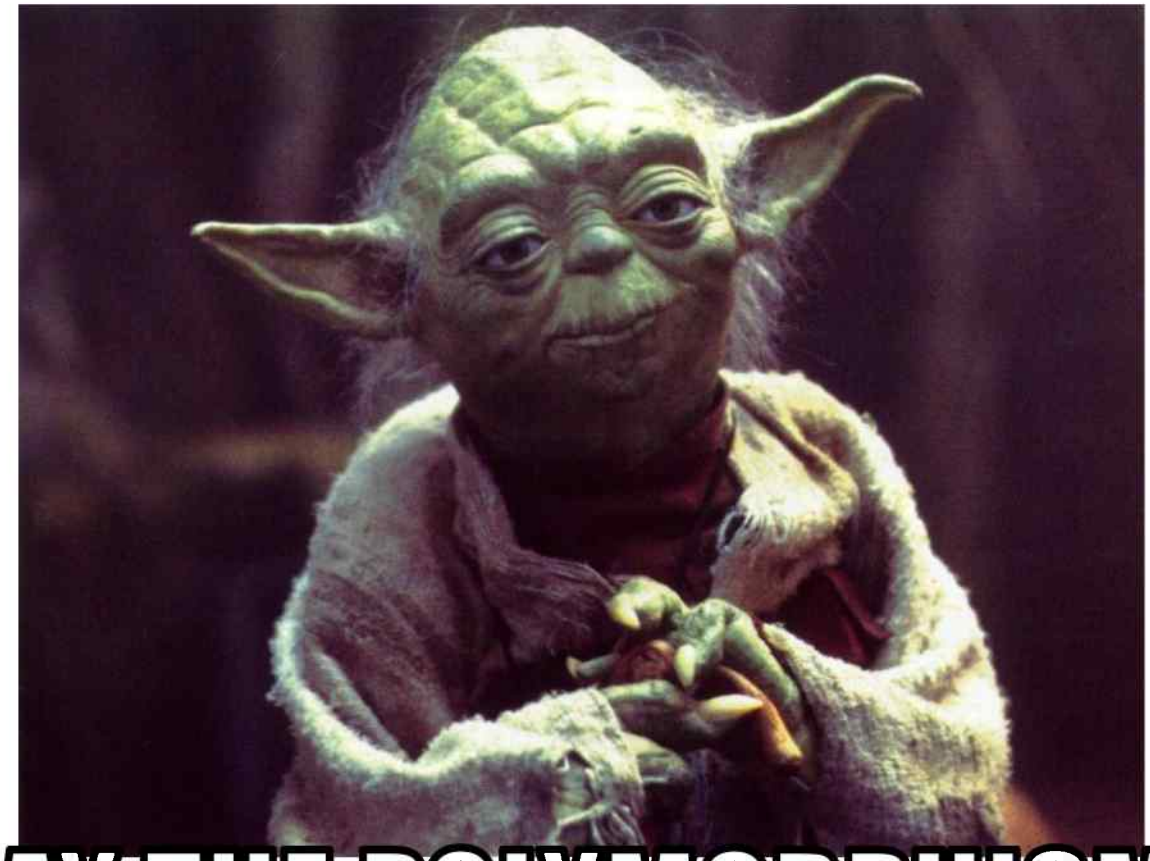
Conclusions

Our study showed a significant correlation between acute severe toxicities and SNPs (XRCC1, XRCC3 and RAD51)

Screening for SNPs before treatment may help to identify patients who are at increased risk of severe toxicity

This can guide clinicians to personalize treatments, selecting patients that can tolerate and complete therapy and will receive the maximum efficacy with minimal morbidity

THANKS FOR YOUR ATTENTION



MAY THE POLYMORPHISMS BE WITH YOU