

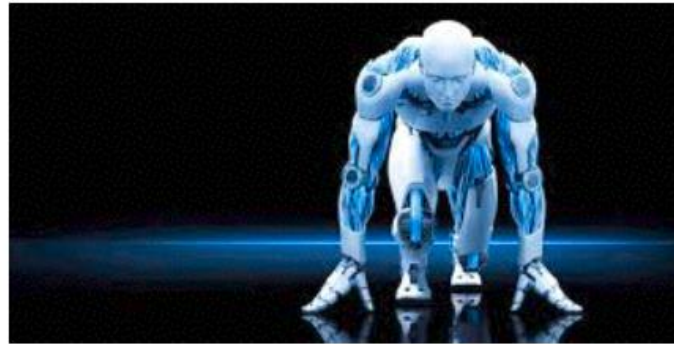


A Beneficência
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LUDWIG
INSTITUTE
FOR
CANCER
RESEARCH

The Surgeon of the future...



Rodrigo Oliva Perez
Instituto Angelita & Joaquim Gama
University of São Paulo Brazil

Technology



Planning



Technology



Planning
Practice



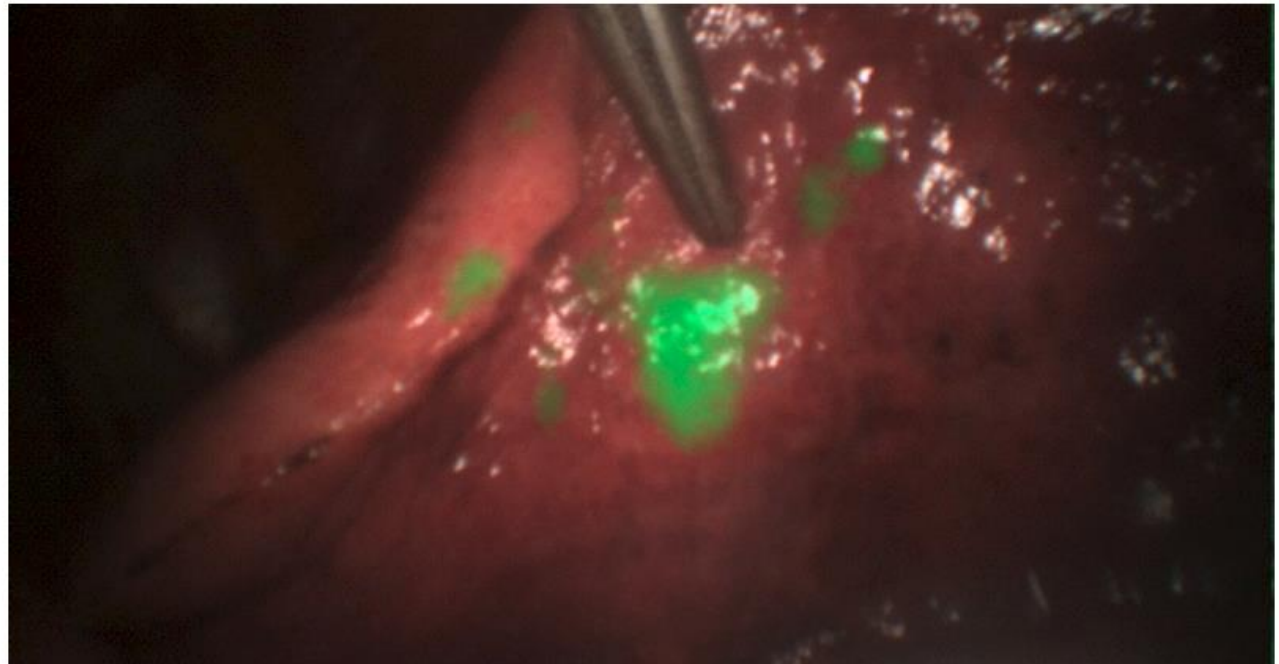
Technology



Planning

Practice

Performance



Technology



Technology

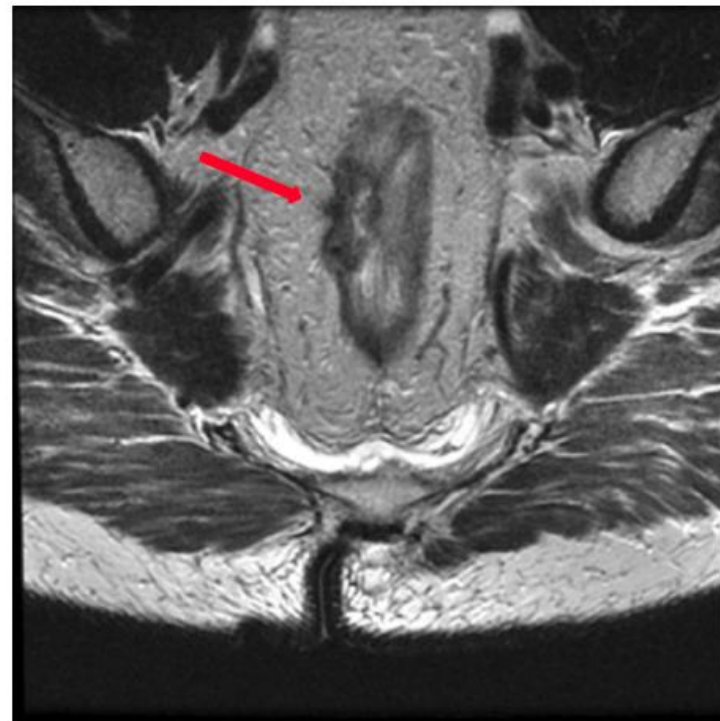
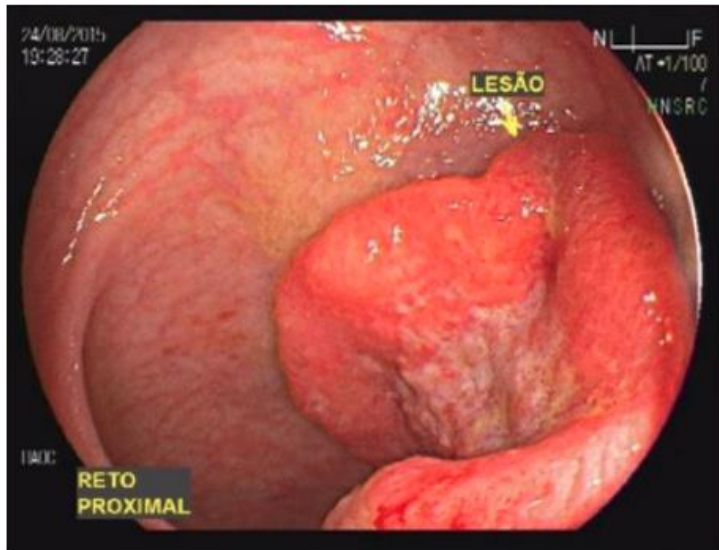


ONE SIZE FITS
ALL: GREAT FOR
SOCKS, BAD
FOR BELIEFS.

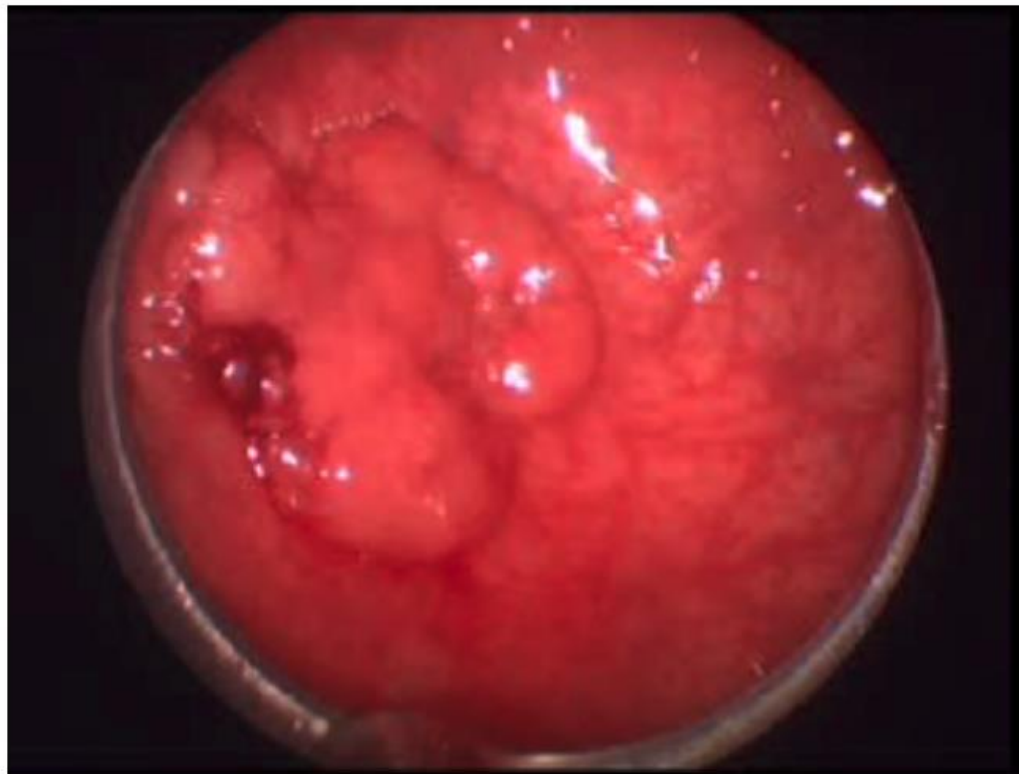
quote from *Act Accordingly*
by Colin Wright



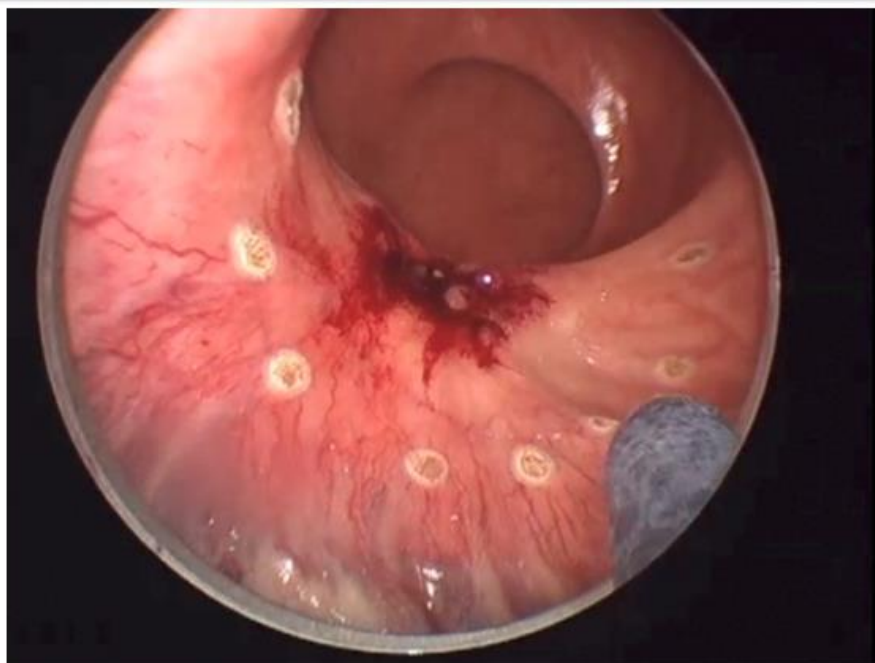
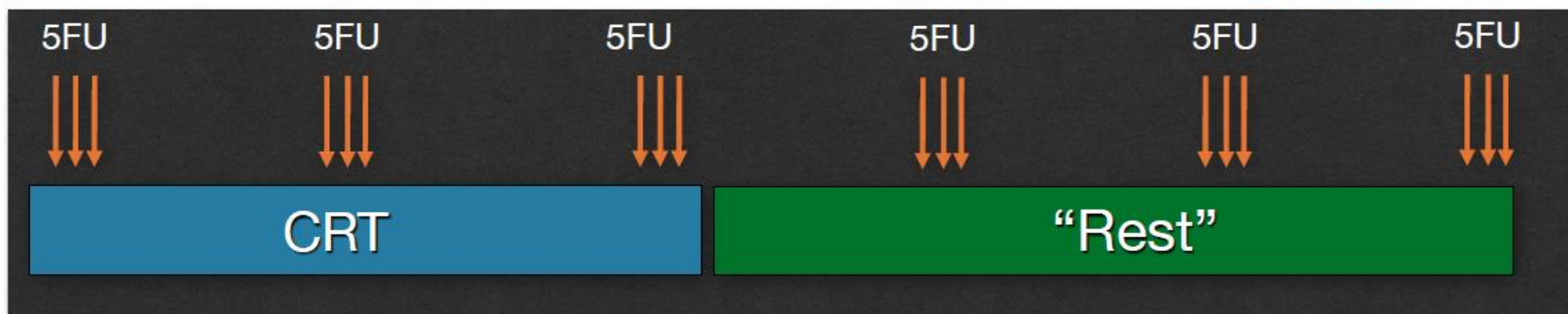
Precision Surgery & Precision Medicine



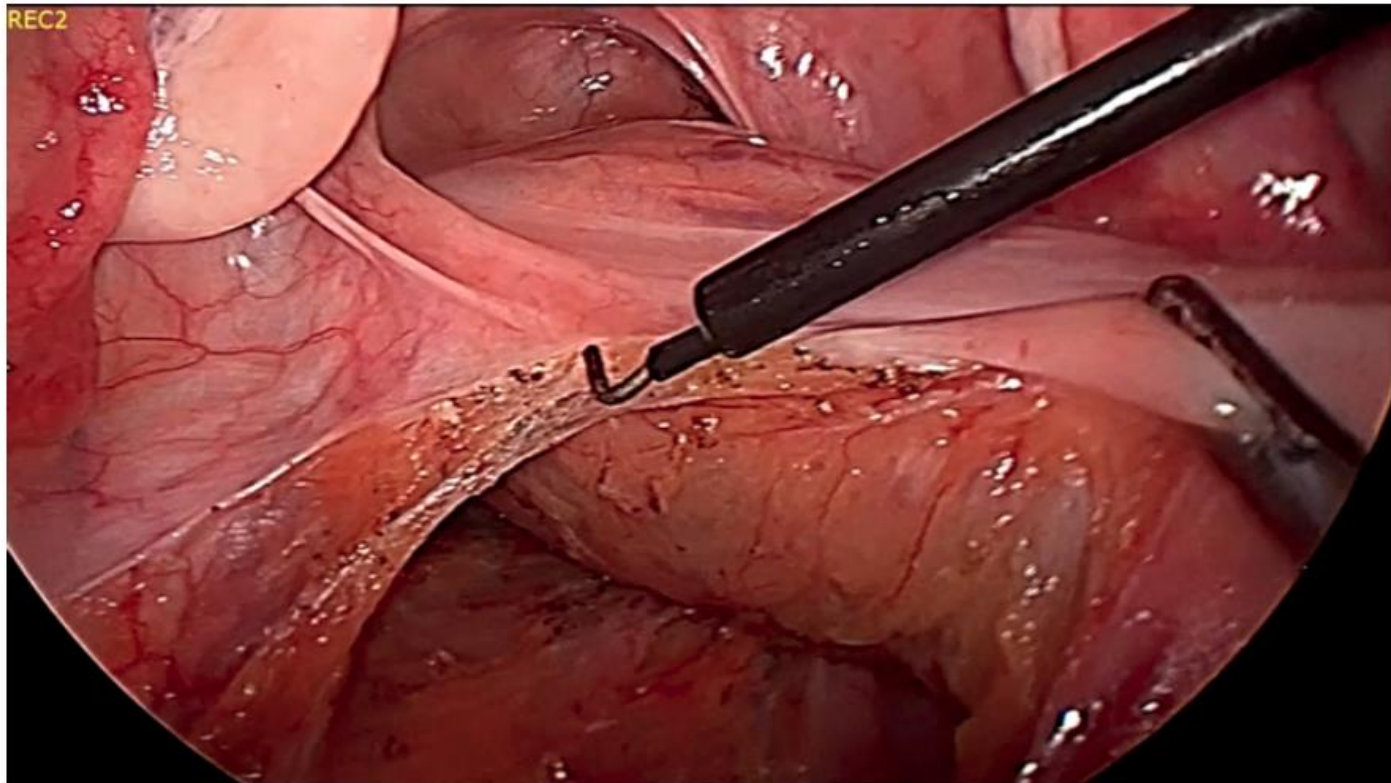
Precision Surgery & Precision Medicine



Precision Surgery & Precision Medicine



Precision Surgery & Precision Medicine



Precision Surgery & Precision Medicine



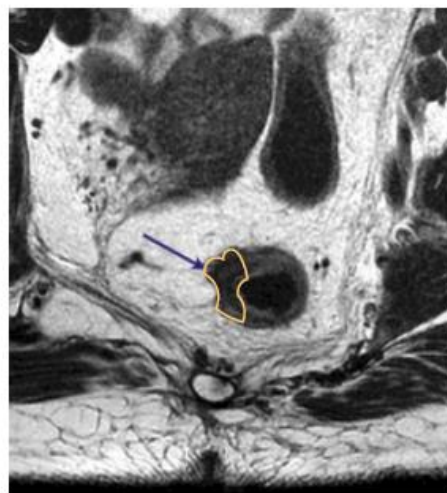
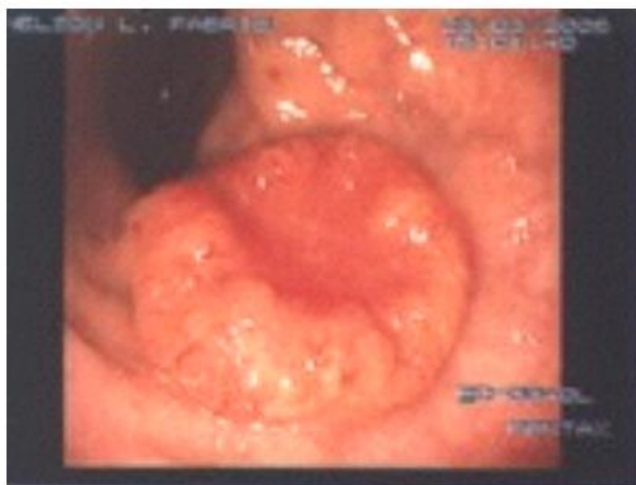
Cancers requiring Extended Lymphadenectomies



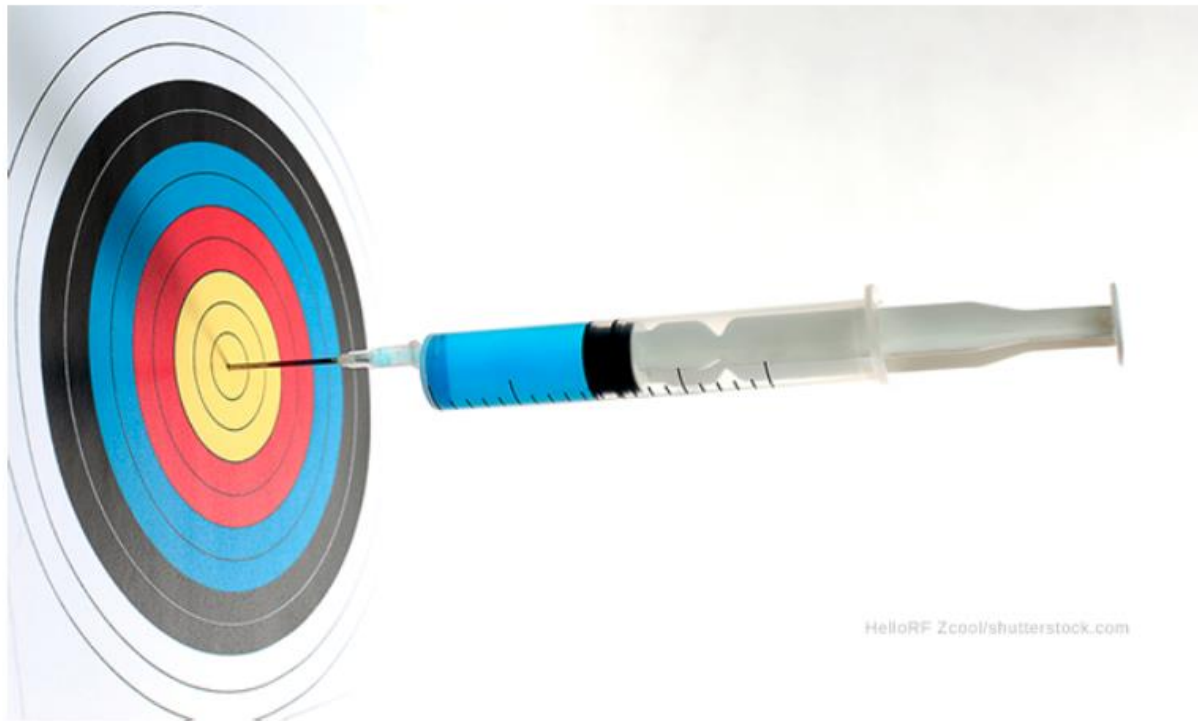
Precision Surgery & Precision Medicine



Cancers requiring No surgery...



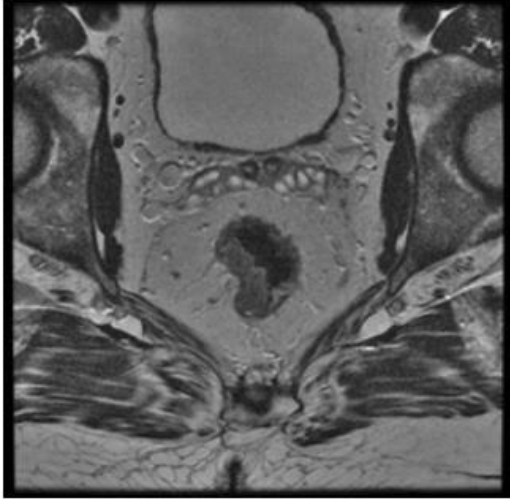
Precision Surgery & Precision Medicine



HelloRF Zcool/shutterstock.com

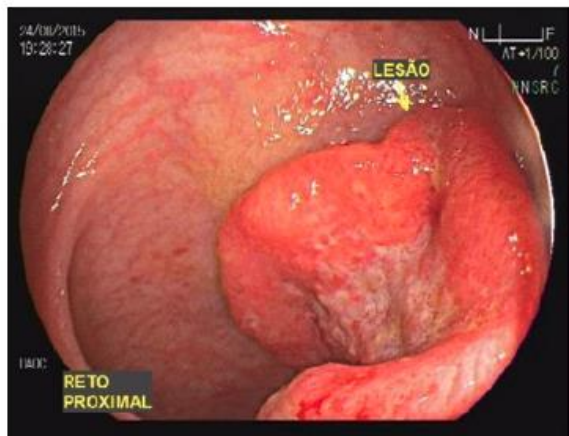
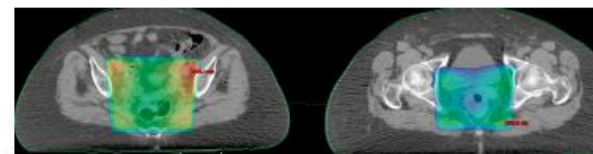
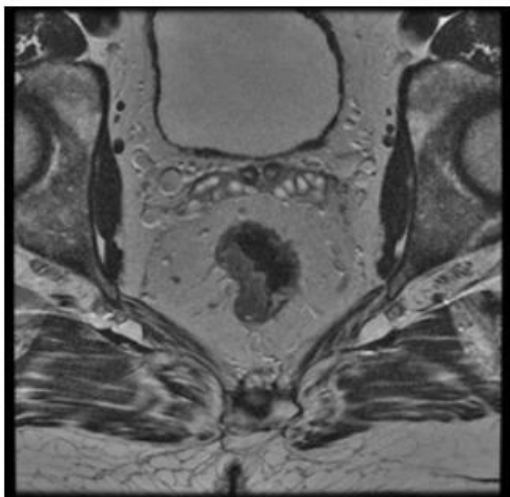
Pre-treatment Biopsies...

Management



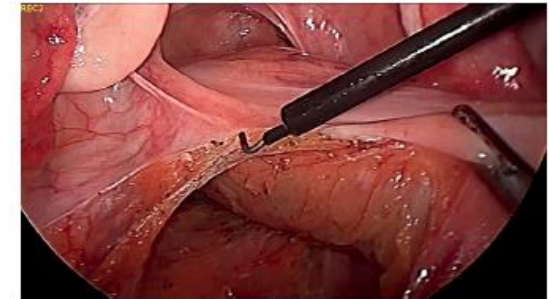
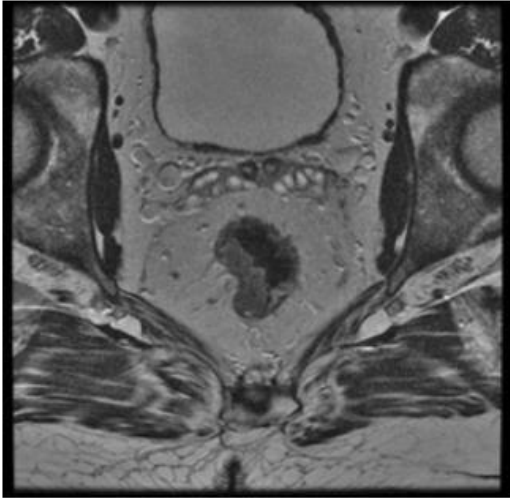
Pre-treatment Biopsies...

Management



Pre-treatment Biopsies...

Management



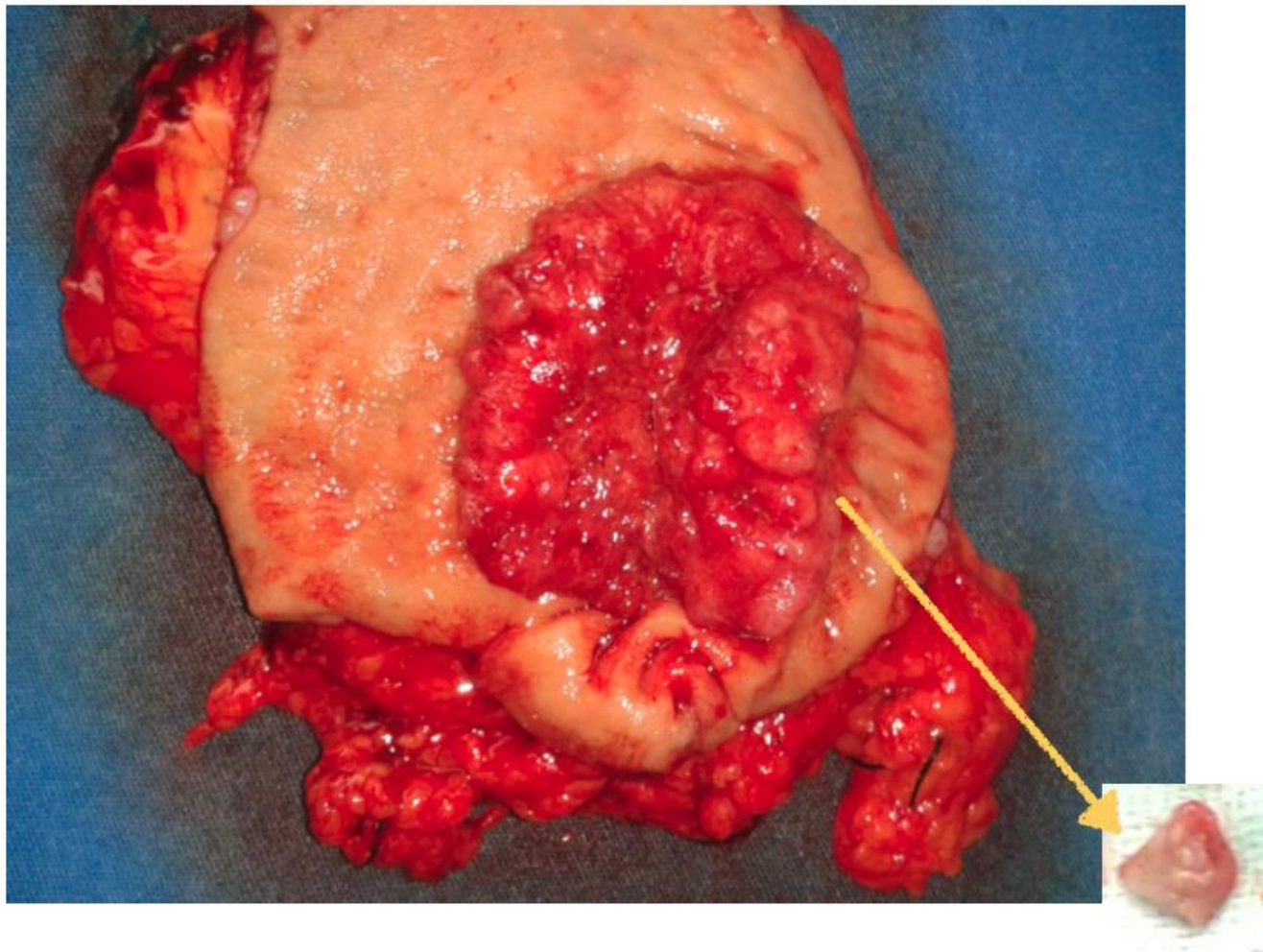
Pre-treatment Biopsies

Predicting Response...

Should We Give Up The Search for a Clinically Useful Gene Signature for the Prediction of Response of Rectal Cancer to Neoadjuvant Chemoradiation?

Rodrigo O. Perez, M.D., Ph.D.
Angelita Habr-Gama, M.D., Ph.D.

not develop complete clinical response (and therefore are not fit for organ-preserving strategies) still require major



Response Prediction

Gene expression

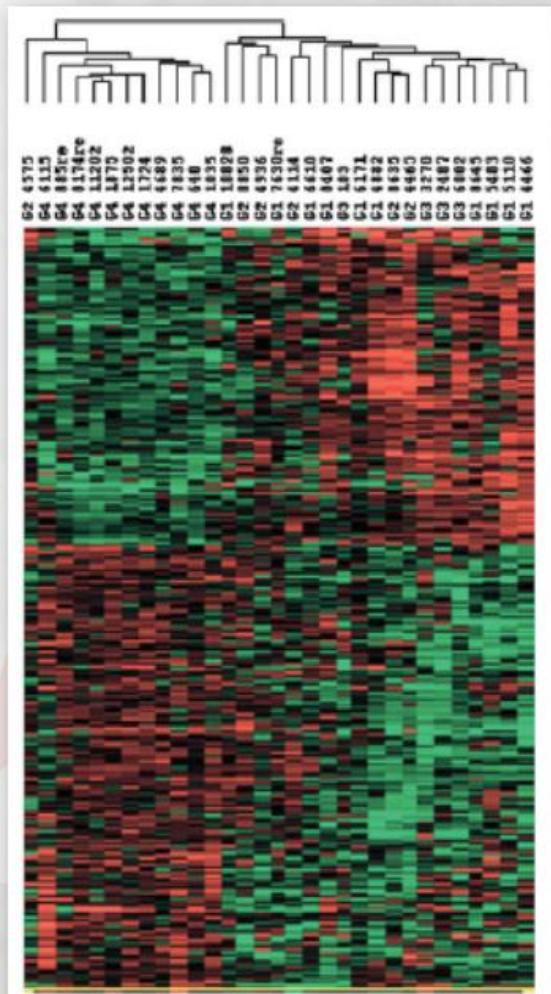
Diseases of the
Colon & Rectum

2007

Microarray Gene Expression Profiling for Predicting Complete Response to Preoperative Chemoradiotherapy in Patients with Advanced Rectal Cancer

Il-Jin Kim, Ph.D.,¹ Seok-Byung Lim, M.D.,² Hio Chung Kang, Ph.D.,²
Hee Jin Chang, M.D.,² Sun-A Ahn, B.S.,¹ Hye-Won Park, M.S.,¹ Sang-Geun Jang, B.S.,¹
Jae-Hyun Park, M.S.,¹ Dae Yong Kim, M.D.,² Kyung Hae Jung, M.D.,²
Hyo Seong Choi, M.D.,² Seung-Yong Jeong, M.D.,² Dae Kyung Sohn, M.D.,²
Duck-Woo Kim, M.D.,¹ Jae-Gahb Park, M.D., Ph.D.¹

Perfil de Expressão



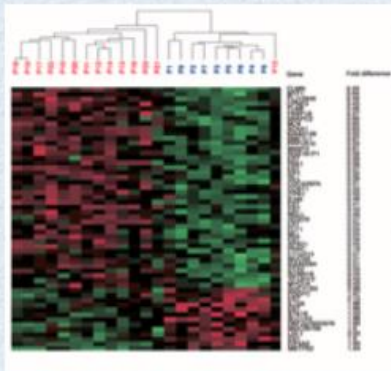
95 genes
Prediction of Response
Accuracy 85%



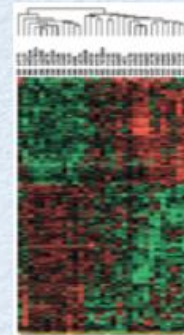
Limitations

Gene signatures don't have a single gene in common?!?!?

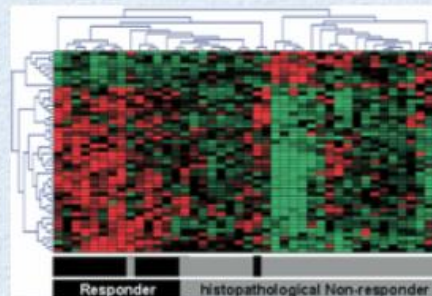
Gadhimi et al



Kim et al



Rimkus et al



Prediction of Tumor Response

Problems?



Studies	# of cases Training - Validation	# of Genes predicting Response
Ghadimi et al. 2005	30 - 7	54
Watanabe et al 2006	52 - 17	33
Kim et al. 2007	46 - 15	95
Rimkus et al. 2008	43	42
Brettingham-Moore et al .2011	51	NI
Nishioka et al. 2011	20 - 3	17
Chan et al. 2013	31	3
Gant et al. 2013	33 - 10	812
Watanabe et al. 2014	62 - 12	4
Palma et al. 2014	26 - 24	257
Nakao S-1 et al. 2015*	30	184
Nakao UFT et al. 2015*	29	193
Lopez-Ramos et al. 2015	25 - 11	27
Empuku et al. 2016	26	80
Milino et al. 2016	58 - 21	256
Gim TO et al. 2016**	77	98
Gim MI et al. 2016**	77	65

15 studies; 17 Gene-Signatures



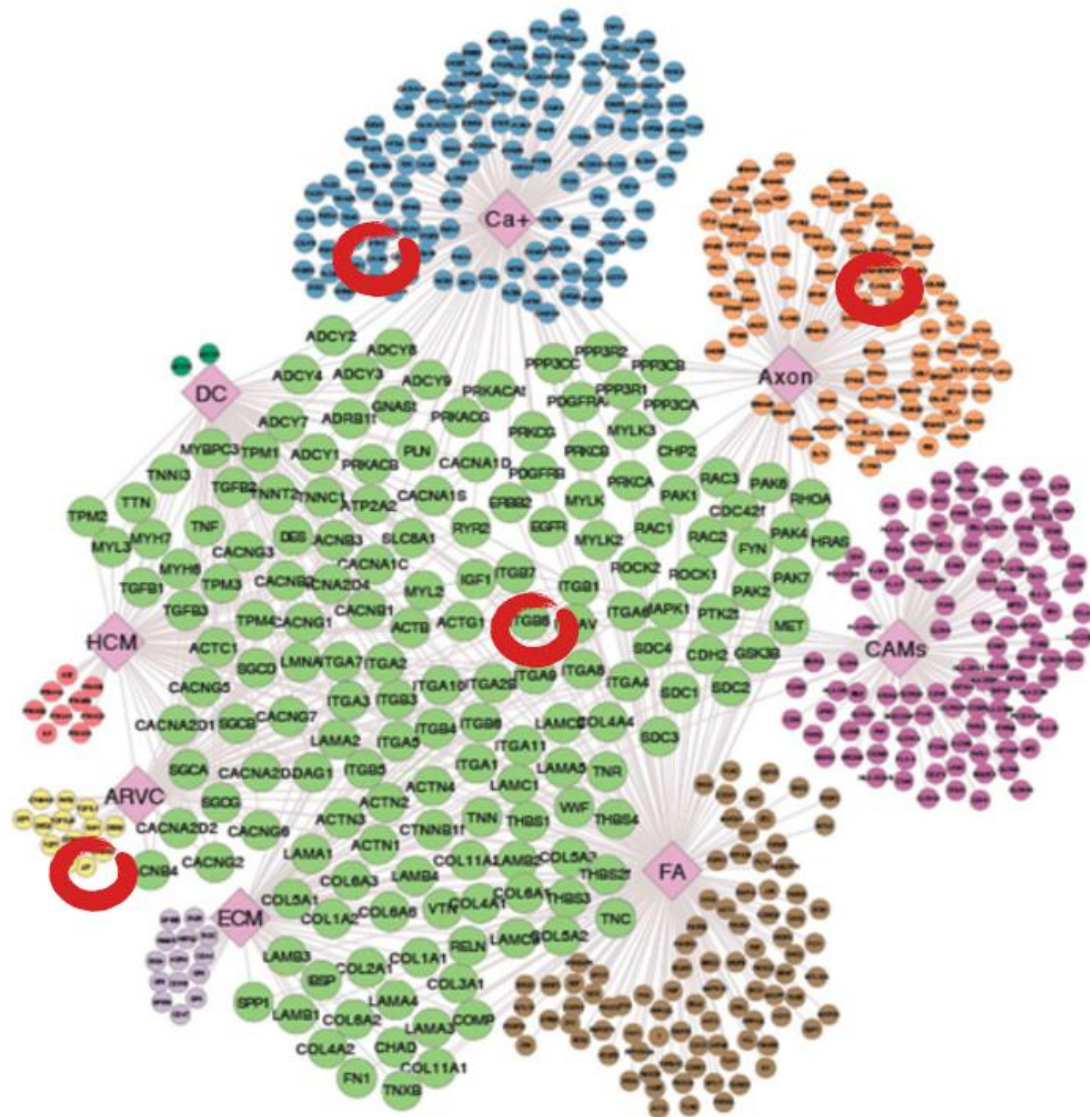
Prediction of Tumor Response

Gene overlap between signatures

Ghadimi	54												
Watanabe	0	33											
Kim	0	FLNA	95										
Rimkus	0	0	0	42									
Nishioka	0	0	MMP14	0	17								
Chan	0	0	0	0	0	3							
Palma	0	0	0	0	0	0	257						
Lopez	FLNB ITPK1 MYO1A	0	0	0	0	0	0	27					
Empuku	0	0	0	0	0	0	0	0	80				
Milino	KIAA0284	0	MCFL RAPGEF 2	0	ITGA2	0	0	0	0	256			
Gim MI	0	0	RPS4Y1	0	0	0	FAM33A	0	0	FUNDC 2	65		
Gim TO	0	0	AP2B1 TPM4	FREM1	0	0	APC	FABP6	0	0	SFT2D2	98	
	Ghadimi	Watanabe	Kim	Rimkus	Nishioka	Chan	Palma	Lopez	Empuku	Milino	Gim MI	Gim TO	

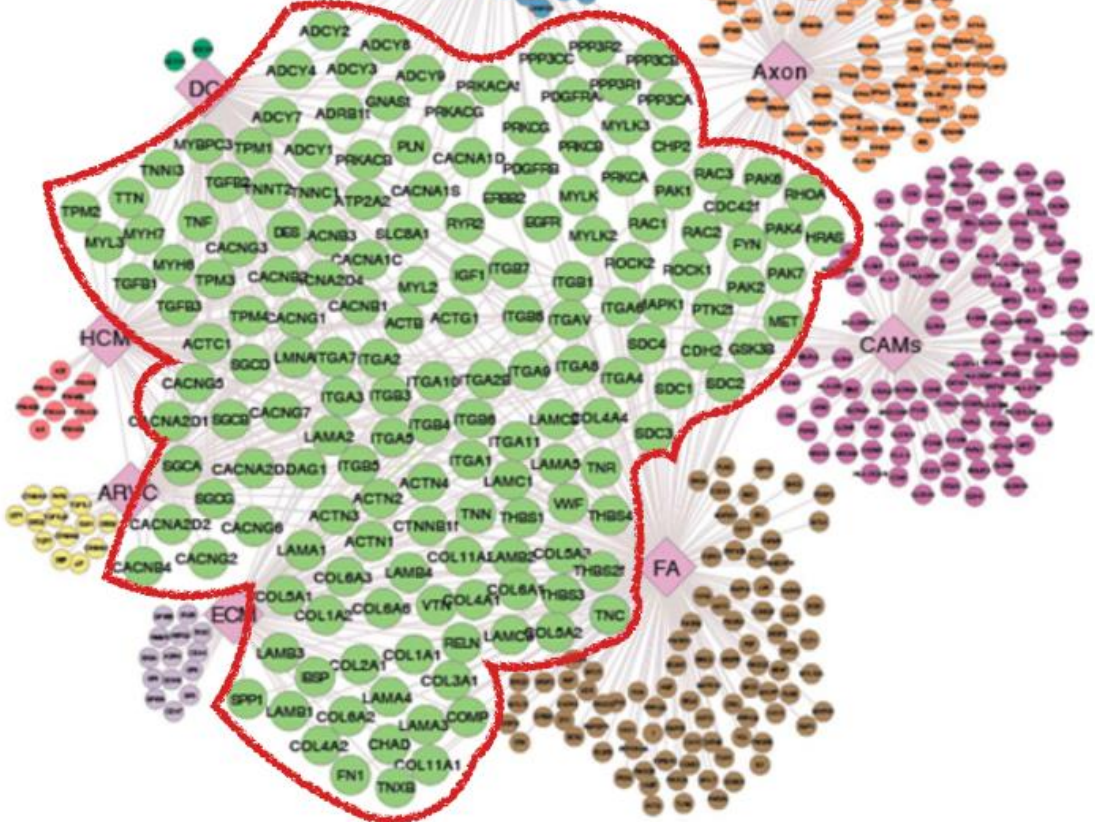
1000 genes! $\leq 2\%$ gene-overlap!!!!

Individual Genes x Pathways Scores



Scores

DNA LESIONS



Individual Genes x **Pathways**

DNA repair

DNA DAMAGING AGENTS

Ionizing radiation
X-rays
Anti-tumor drugs



DNA LESIONS

Double strand breaks
Single strand breaks
Intrastrand crosslinks
Interstrand crosslinks

Individual Genes x Pathways

DNA repair

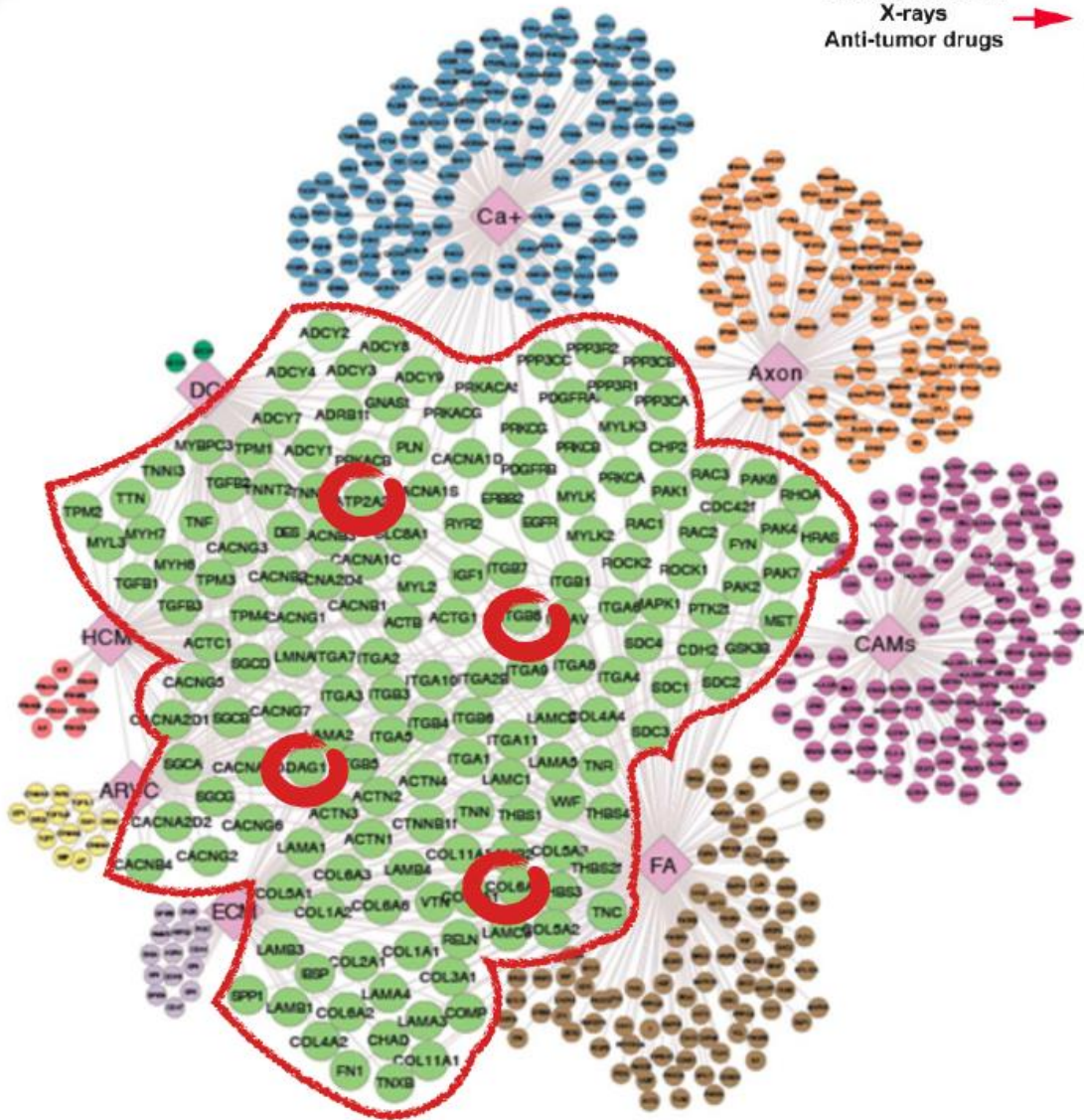
DNA DAMAGING AGENTS

DNA LESIONS

Ionizing radiation
X-rays
Anti-tumor drugs

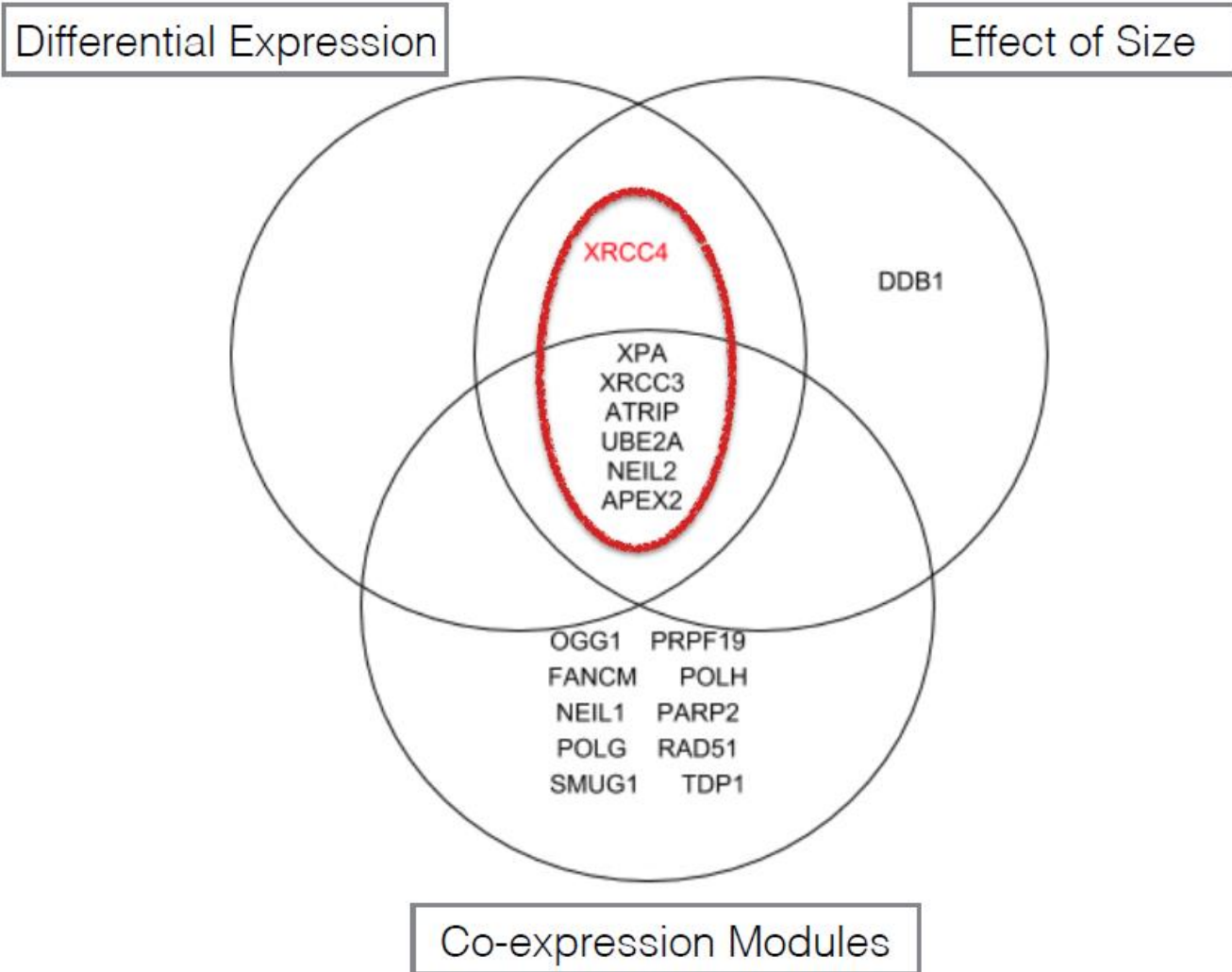


Double strand breaks
Single strand breaks
Intrastrand crosslinks
Interstrand crosslinks



Score

Selection of Genes



Calculations

Deregulation Score

Differentially expression data

8 Genes (DNA repair)

RPKM: measure of gene-expression

Up-regulated genes

Down-regulated genes

RPKM $\times +1$

+

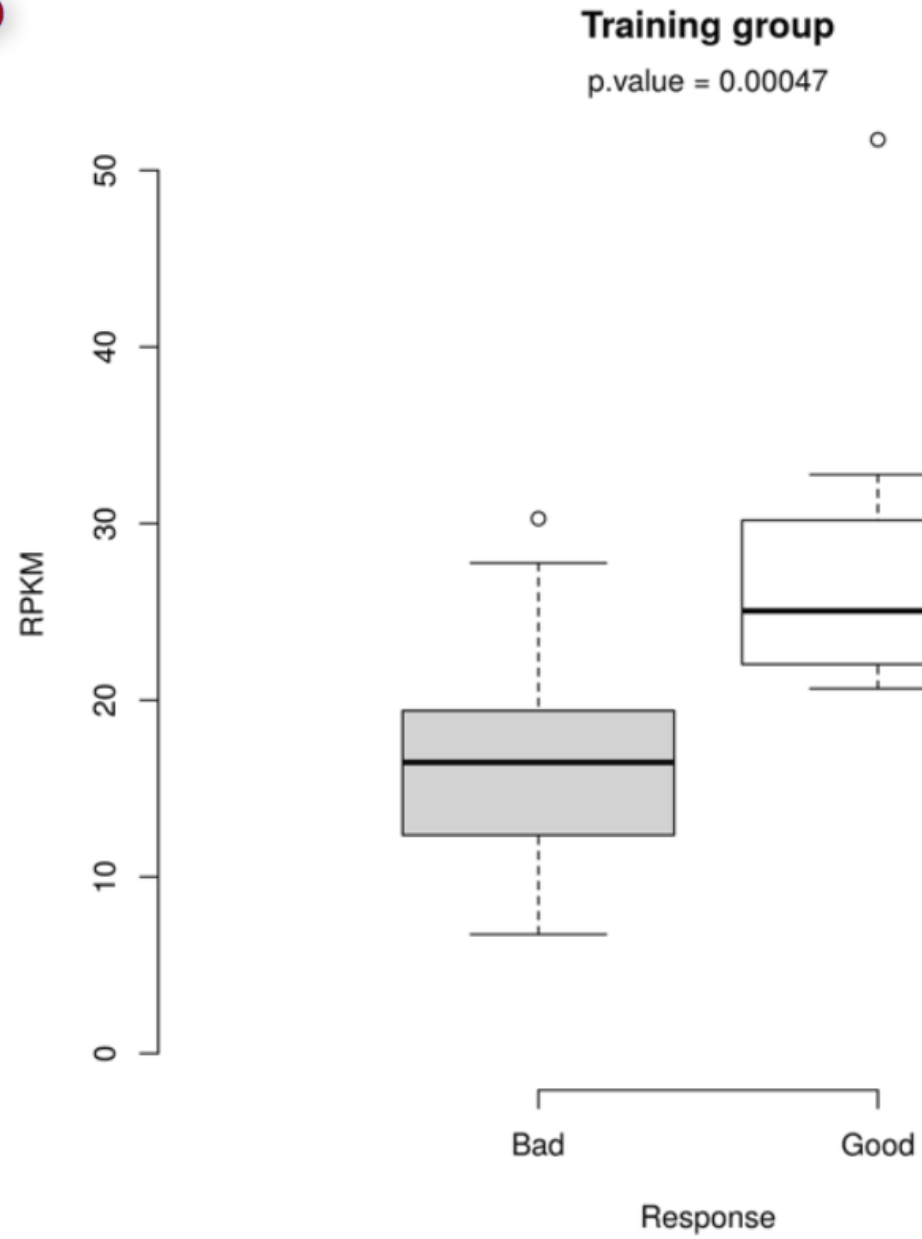
RPKM $\times -1$

Deregulation Score for each individual patient

Good X Bad Response

Training Group

25 patients
9 CR's
16 Incomplete

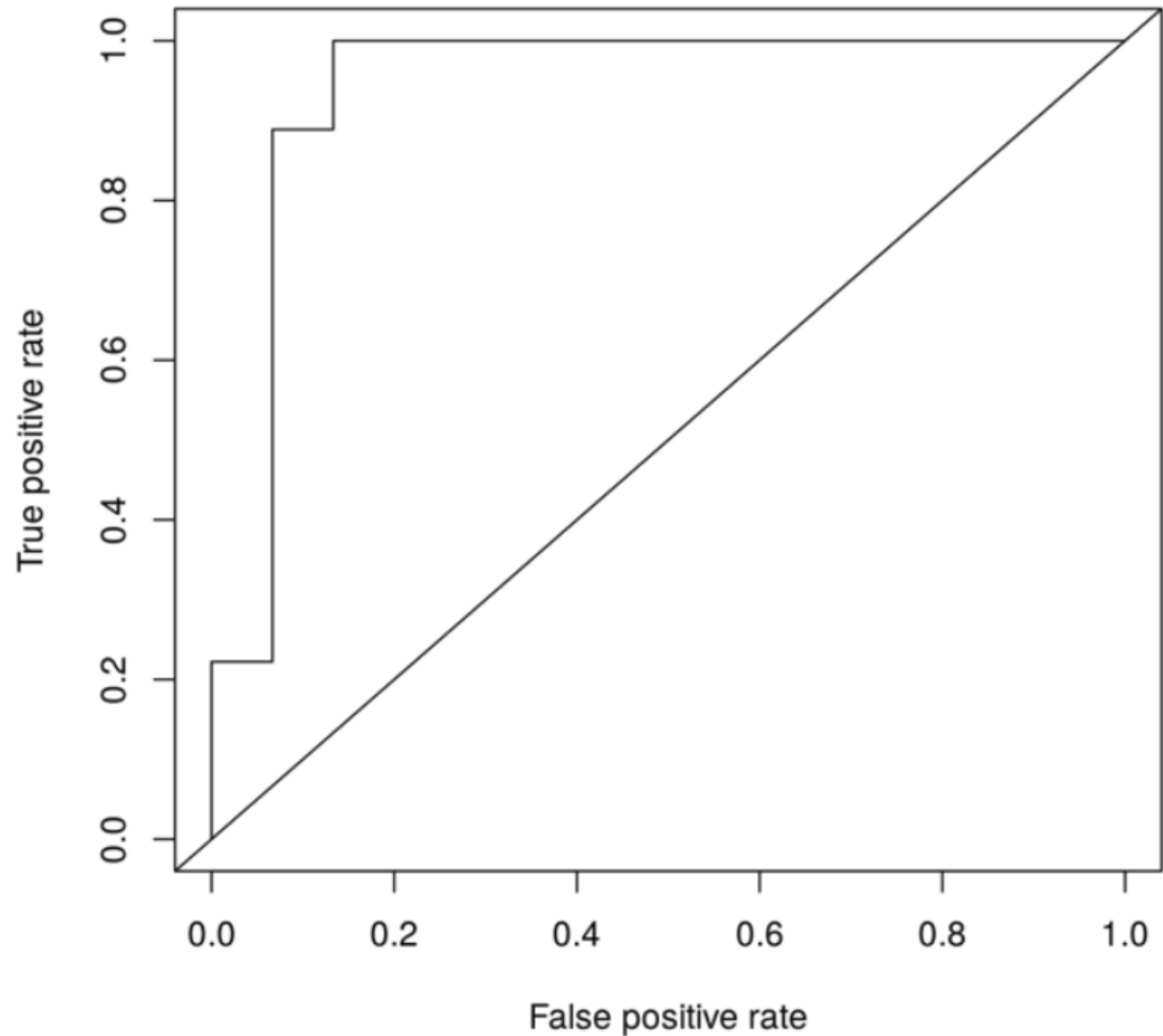


Prediction of Response

Deregulation Score

ROC curve training group

AUC=0.94
Cutoff=19.5
Sensitivity:87%
Specificity:100%



Good X Bad Response

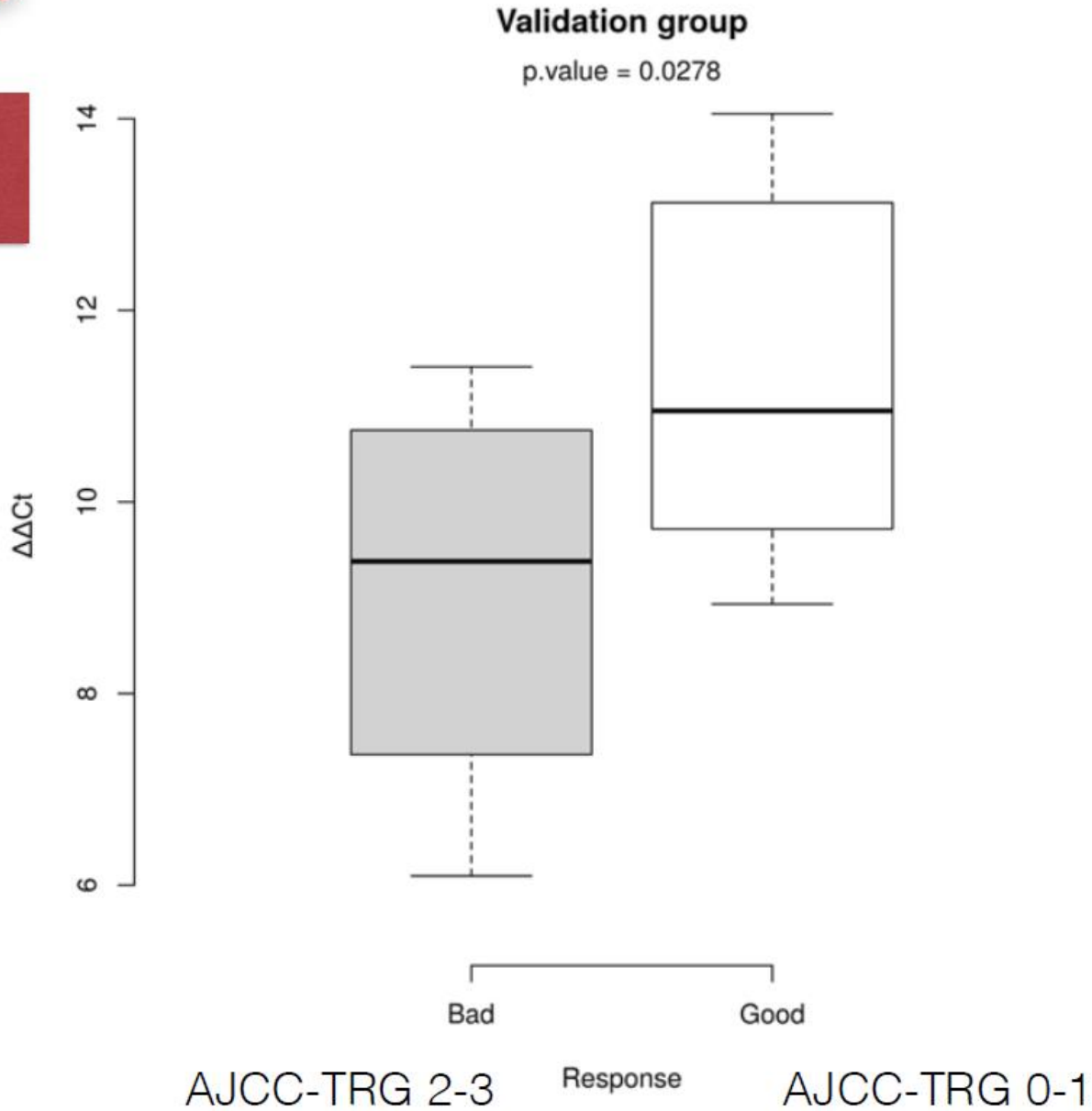
Validation Group

Independent sample of patients (CCF-Ohio)
Similar nCRT
Pathological endpoint (TRG - AJCC)
qRT-PCR

Good X Bad Response

Validation Group

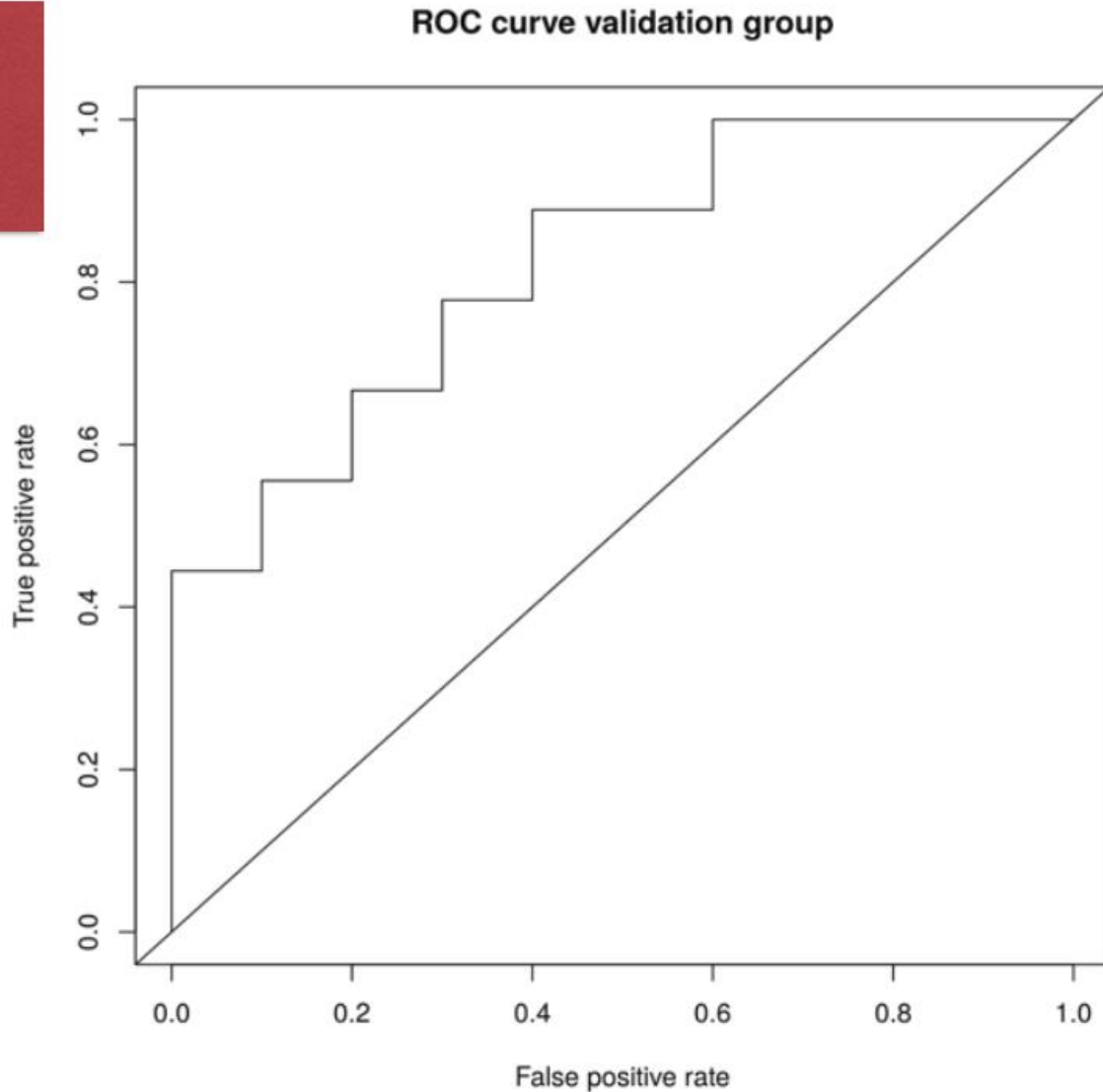
21 patients
7 Good (AJCC 0-1)
14 Bad (AJCC 2-3)



Prediction of Response

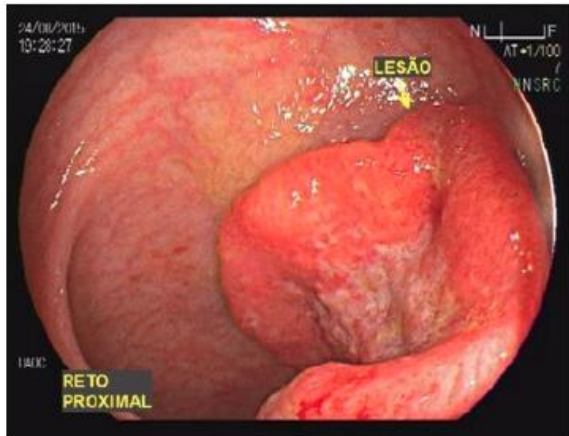
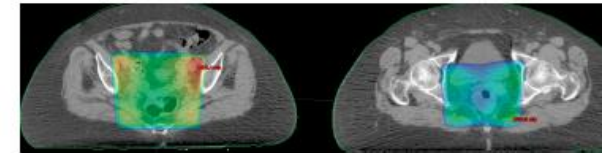
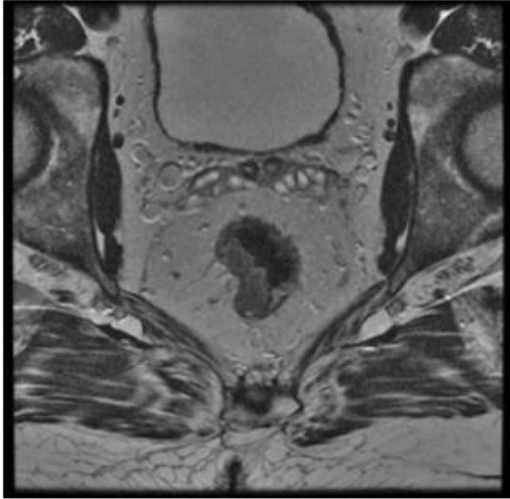
Deregulation Score

AUC=0.85
Cutoff=10.7
Sensitivity:62.5%
Specificity:92.3%



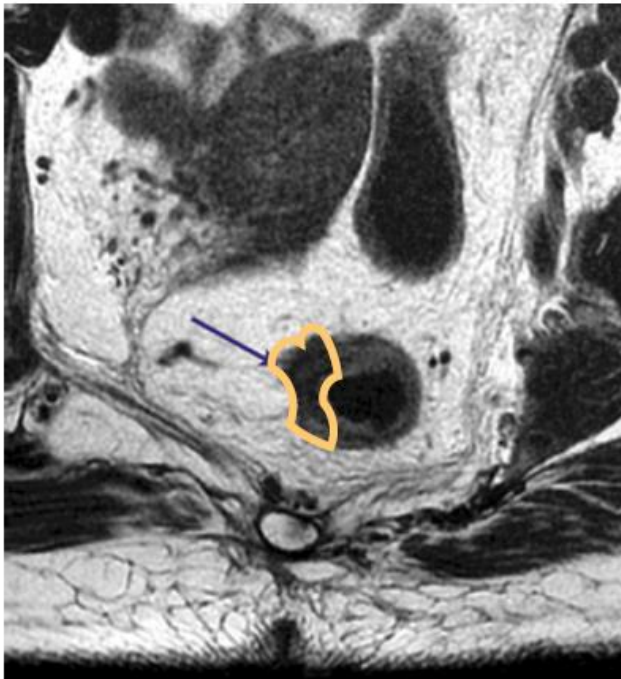
Pre-treatment Biopsies...

Management



Pre-treatment Biopsies...

Management



ctDNA

Rearrangements



Contents lists available at ScienceDirect

2015

Genomics

journal homepage: www.elsevier.com/locate/ygeno



Methods

ICRmax: An optimized approach to detect tumor-specific interchromosomal rearrangements for clinical application

Elisa R. Donnard^{a,b}, Paola A. Carpinetti^{a,b}, Fábio C.P. Navarro^{a,b}, Rodrigo O. Perez^{c,d}, Angelita Habr-Gama^c, Raphael B. Parmigiani^a, Anamaria A. Camargo^{a,d}, Pedro A.F. Galante^{a,*}

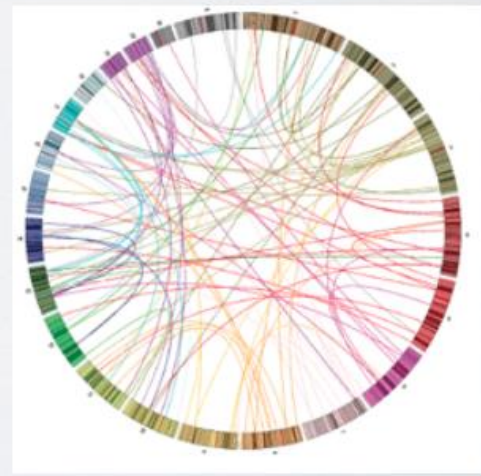


DNA
Sequence

Patient #1

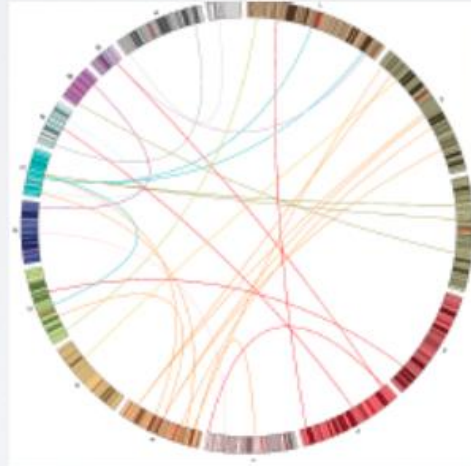
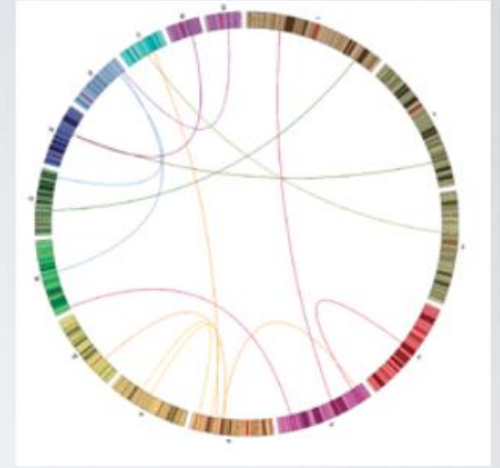
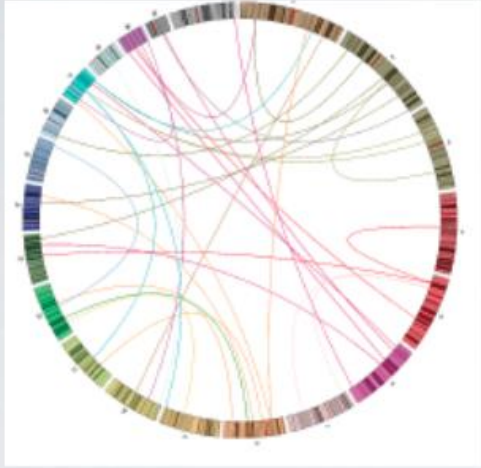


Patient #2



ctDNA

Rearrangements



ctDNA Rearrangements

www.impactjournals.com/oncotarget/

Oncotarget, Advance Publications 2015

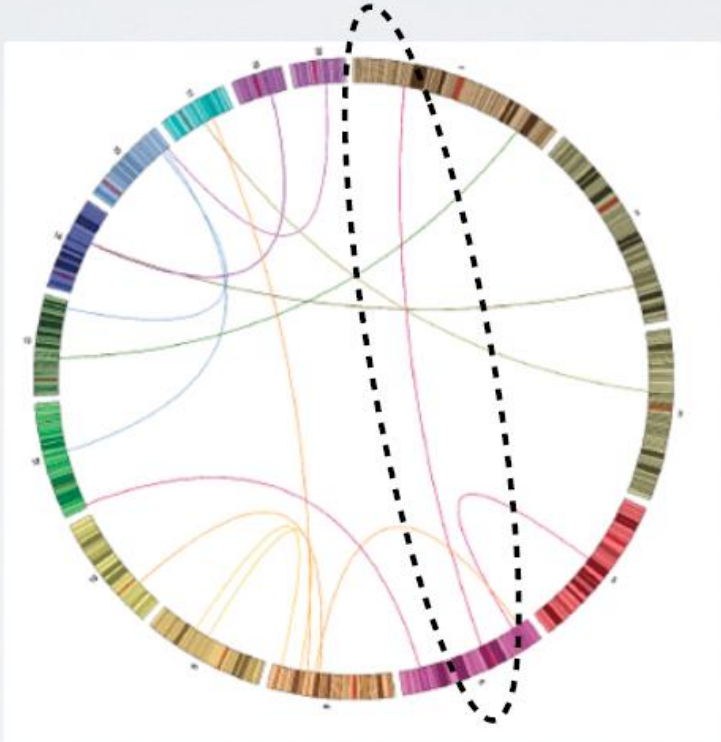
The use of personalized biomarkers and liquid biopsies to monitor treatment response and disease recurrence in locally advanced rectal cancer after neoadjuvant chemoradiation

Paola Carpinetti^{1,2,3}, Elisa Donnard^{1,2,3}, Fabiana Bettoni², Paula Asprino², Fernanda Koyama¹, Andrei Rozanski², Jorge Sabbaga⁴, Angelita Habr-Gama^{5,6}, Raphael B. Parmigiani², Pedro A.F. Galante², Rodrigo O. Perez^{1,5,6}, Anamaria A. Camargo^{1,2}

Biopsy Fragment



TSGV Identification

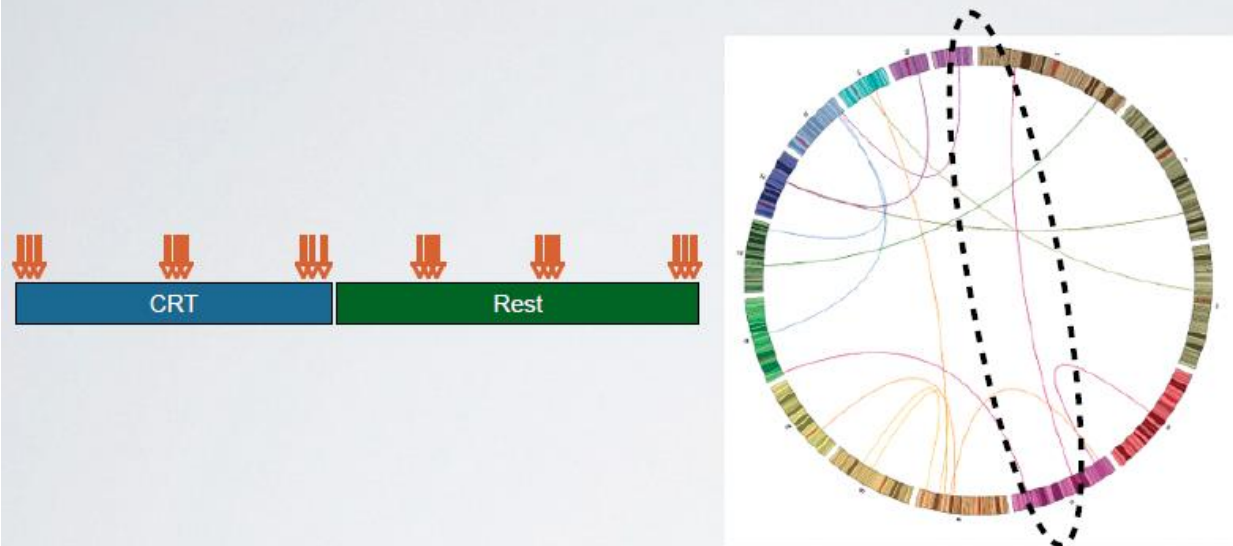


Identification in
Peripheral Blood

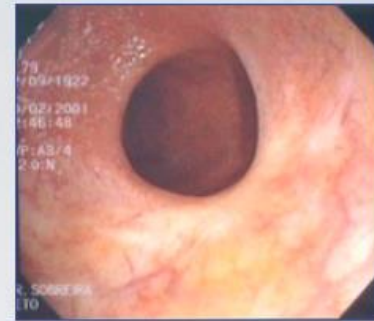


ctDNA

Rearrangements



Negative



Positive



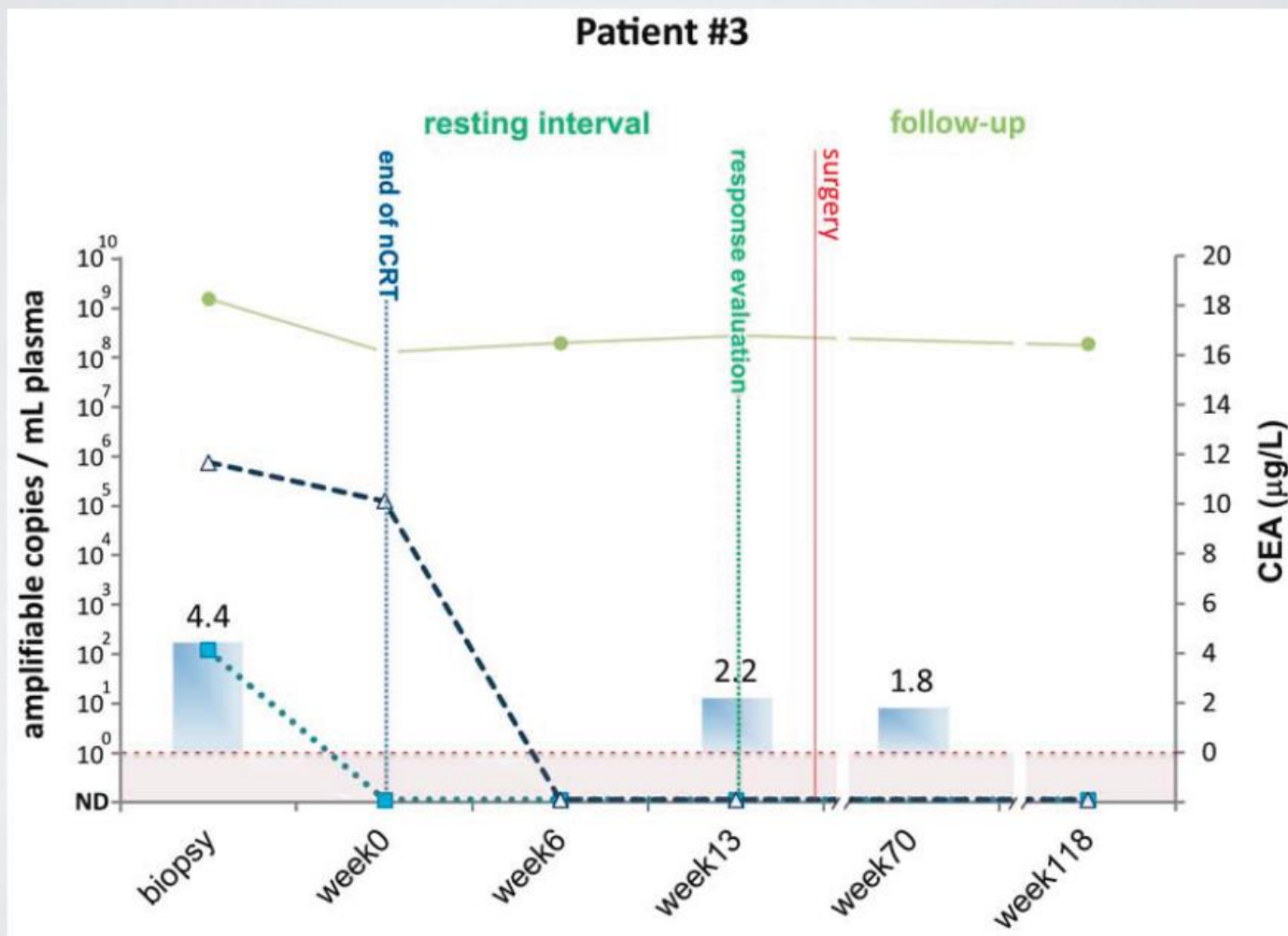
Each Patient will have his/her own TSGV - marker!!!

Monitoring of Response

Liquid Biopsies

The use of personalized biomarkers and liquid biopsies to monitor treatment response and disease recurrence in locally advanced rectal cancer after neoadjuvant chemoradiation

Paola Carpinetti^{1,2,3}, Elisa Donnard^{1,2,3}, Fabiana Bettoni², Paula Asprino², Fernanda Koyama¹, Andrei Rozanski², Jorge Sabbaga⁴, Angelita Habr-Gama^{3,6}, Raphael B. Parmigiani², Pedro A.F. Galante², Rodrigo O. Perez^{1,5,6}, Anamaria A. Camargo^{1,2}



Prediction of Response?



Monitoring of Response?



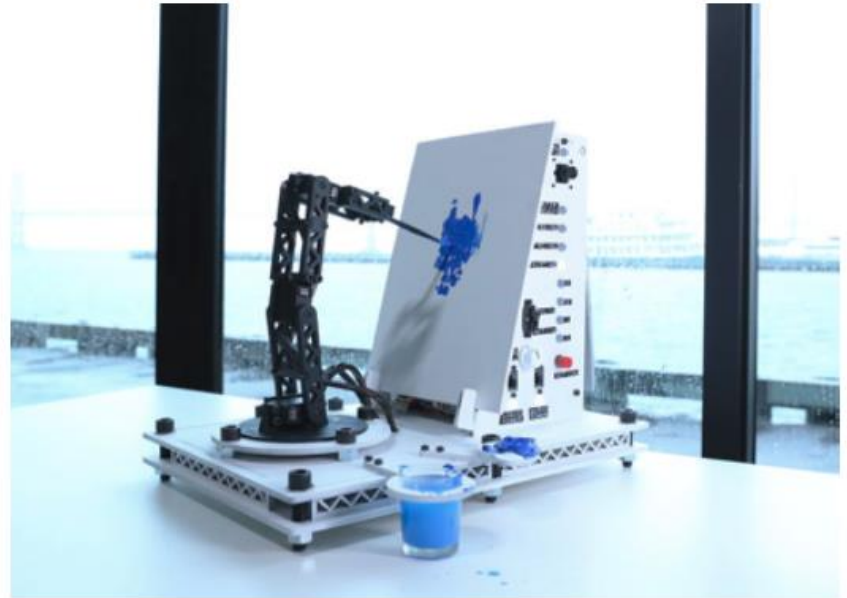
Future of Surgery

Not all about technology itself...



Future of Surgery

Not all about technology itself...



Future of Surgery

Not all about technology itself...



Future of Surgery

Not all about technology itself...

