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Radiation Oncology

RSI:

A genomic signature of radiosensitivity

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Disclosures

- Clinical Advisory Board, Novocure

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RSI

- Molecular signature of tumor radiosensitivity
  - extensive clinical and analytical validation
- Linear regression equation developed to correlate gene expression and SF2
  - 48 cell lines.
  - Final algorithm involves 10 genes
  - validated in 12 independent datasets totaling over 2,200 patients
    - Various cancers,
    - International data

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 2, pp. 497–505, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2009.05.056

BIOLOGY CONTRIBUTION

SYSTEMS BIOLOGY MODELING OF THE RADIATION SENSITIVITY NETWORK: A BIOMARKER DISCOVERY PLATFORM

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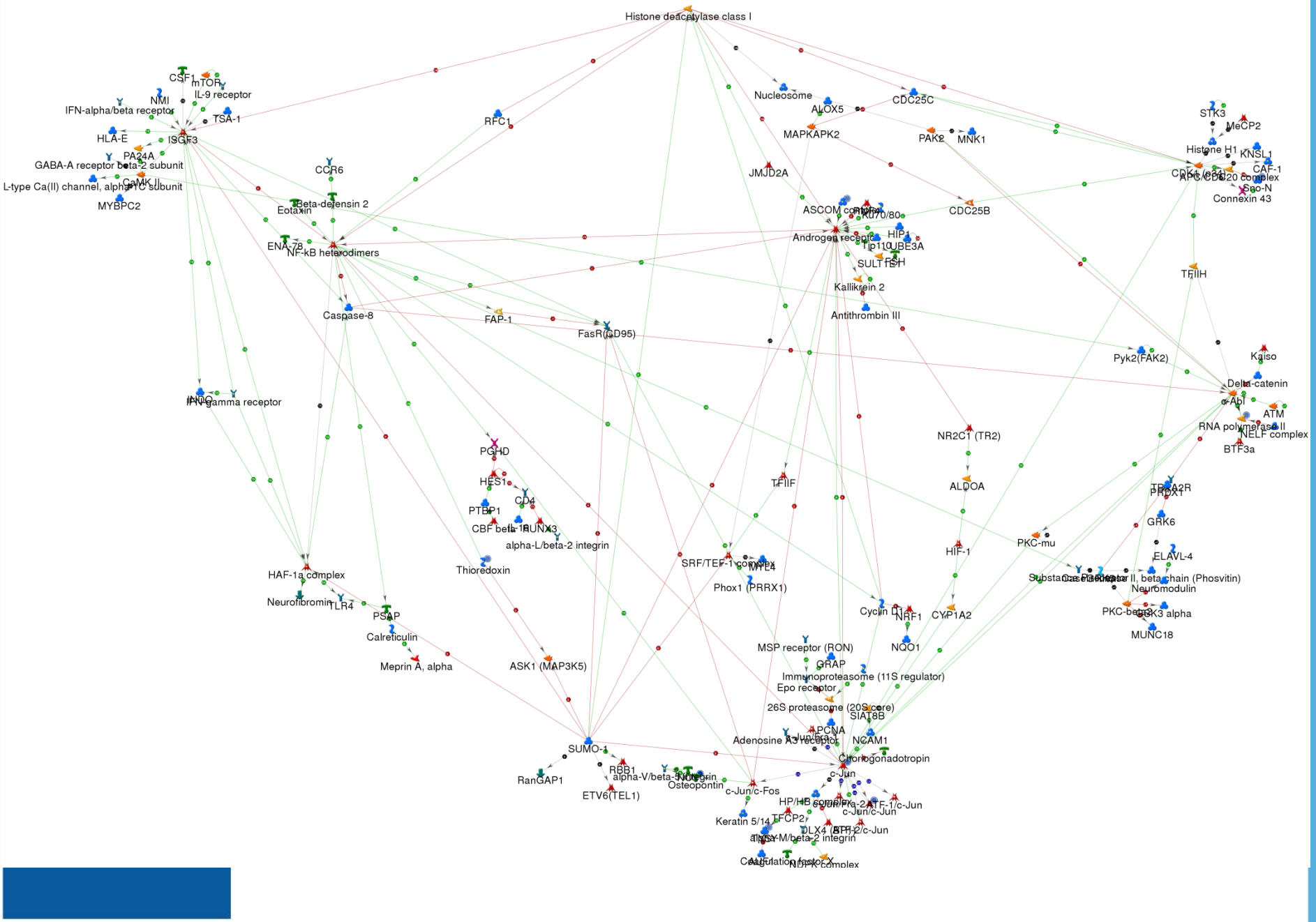
Histone deacetylase class I
CSF1
mTOR
IL-9 receptor
NMI
IFN-alpha/beta receptor
TSA-1
HLA-E
ISGF3
PA24A
GABA-A receptor beta-2 subunit
CaMK II
L-type Ca(II) channel, alpha-1C subunit
MYBPC2
RFC1
CCR6
Eotaxin
Beta-defensin 2
ENA-78
NF-kB heterodimers
Caspase-8
FAP-1
FasR(CD95)
IRDC
IFN-gamma receptor
PGHD
HES1
CD4
PTBP1
CBF beta-1
RUNX3
alpha-L/beta-2 integrin
Thioredoxin
HAF-1a complex
Neurofibromin
TLR4
PSAP
Calreticulin
Meprin A, alpha
ASK1 (MAP3K5)
SUMO-1
RanGAP1
RBB1
ETV6(TEL1)
alpha-V/beta-5 integrin
Osteopontin
c-Jun/c-Fos
Keratin 5/14
TFCP2
DLX4
alpha-M/beta-2 integrin
Coagulation factor X
NF-K complex
Nucleosome
ALOX5
CDC25C
MAPKAPK2
PAK2
MNK1
JMJD2A
CDC25B
ASCOM complex
Ku70/80
Androgen receptor
HIP1
Tip110
UBE3A
SULT1E1
Kallikrein 2
Antithrombin III
TFIIF
SRF/TEF-1 complex
MYL4
Phox1 (PRRX1)
NR2C1 (TR2)
ALDOA
HIF-1
Cyclin D1
NRF1
CYP1A2
NQO1
MSP receptor (RON)
GRAP
Immunoproteasome (11S regulator)
Epo receptor
26S proteasome (20S core)
SIAT8B
PCNA
Adenosine A3 receptor
Jun/Fos
NCAM1
Chorionogonadotropin
c-Jun
HP/HB complex
ATF-1/c-Jun
c-Jun/c-Jun
BPF-2/c-Jun
STK3
MeCP2
Histone H1
KNSL1
CAF-1
CDK4 (CDK6)
APC/CDC20 complex
Seo-N
Connexin 43
TFIIH
Pyk2(FAK2)
Kaiso
Delta-catenin
c-Abl
ATM
RNA polymerase II
NELF complex
BTF3a
TBRA2R
PRRX1
GRK6
PKC-mu
ELAVL-4
Neuromodulin
PKC-beta
PI3K3 alpha
MUNC18

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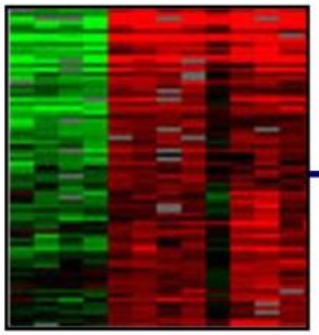
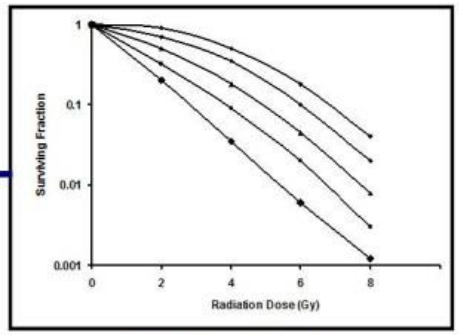


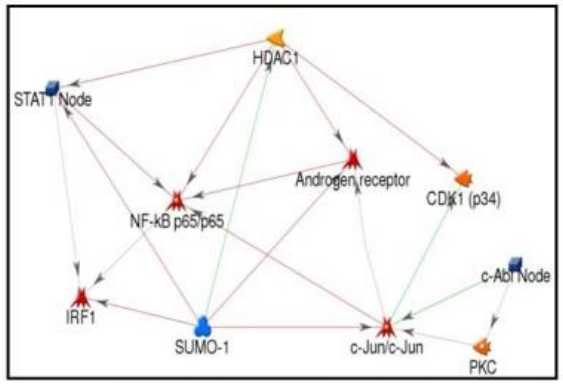
Molecular Scale
Gene Expression

RSI (Radiosensitivity Index) =
k0 + k1(yx) + k2(TO) + k3(ras status)
+ k4(p53 status) + k5(yx)(TO) +
k6(yx)(ras status) + k7(TO)(ras
status) + k8(yx)(p53 status) + k9(TO)(p53)
+ k10(ras status)(p53 status)
+ k11(yx)(TO)(ras status) +…

Pathway Scale
Mathematical Equation



Cellular Scale
Cellular Radiosensitivity



Regulatory Networks
Scale

Torres-Roca J, et al. (2005) Cancer Res 65:7169-76
Eschrich SA et-al (2009) IJROBP 75:489-96
Eschrich SA et al (2009) IJROBP;75:497-505
Eschrich SA eta al (2012) Clin Can Res 18:5134-43
Torres-Roca JF (2012) Per Med 9:547-55

Platform comparison for assay

Gene Expression Platform	Overall Accuracy (Class Prediction)
Microarray (HU 6800)	81%
Microarray (U133Plus)	77%
RT-PCR-Preamplification	81%
RT-PCR-No Preamplification	90%
Nanostring	73%
HT Genomics	81%
FFPE-RT-PCR-Preamplification	79%

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A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized radiation therapy

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RSI

Tissue Type	# Samples	Number RR	% RR	Mean (RSI Score)	Median (RSI Score)	Std	Fisher's Exact p Value
Brain	220	211	95.91	0.58	0.56	0.12	4.59E-38
Thyroid	68	58	85.29	0.48	0.51	0.11	2.78E-06
Soft Tissue	127	104	81.89	0.51	0.51	0.16	1.91E-08
Pancreas	452	348	76.99	0.43	0.45	0.11	4.35E-17
Skin	617	433	70.18	0.45	0.46	0.14	8.56E-10
Uterus	722	498	68.98	0.41	0.43	0.13	2.49E-09
Rectum	163	108	66.26	0.43	0.46	0.13	4.54E-02
Stomach	118	75	63.56	0.41	0.43	0.12	3.02E-01
Bladder	248	154	62.1	0.41	0.43	0.14	2.43E-01
Prostate	197	118	59.9	0.39	0.40	0.11	7.16E-01
Kidney	832	484	58.17	0.40	0.42	0.12	8.85E-01
Ovary	686	397	57.87	0.39	0.42	0.14	7.81E-01
Large Bowel	2,066	1,165	56.39	0.39	0.42	0.11	4.14E-02
Breast	3,790	2,063	54.43	0.39	0.39	0.12	3.98E-09
Lung	2,592	1,392	53.7	0.39	0.40	0.11	5.96E-08
Esophagus	83	44	53.01	0.37	0.41	0.12	3.17E-01
HeadNeck	221	97	43.89	0.37	0.36	0.11	1.29E-05
Cervix	65	23	35.38	0.35	0.31	0.10	2.08E-04
Liver	69	21	30.43	0.30	0.30	0.13	3.38E-06
Totals:	**13,336**	**7,793**					

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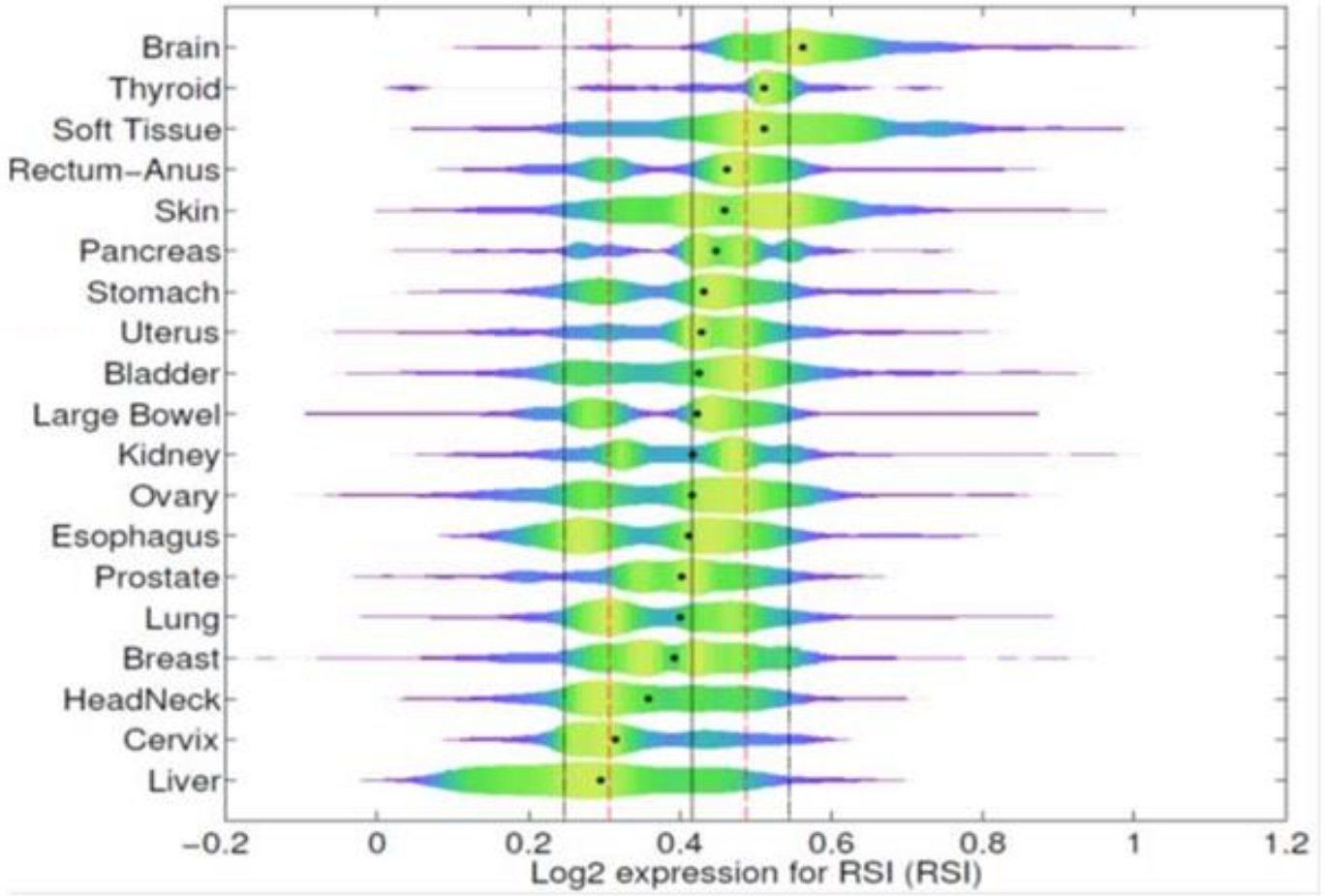
RSI



Torres-Roca JF et al (2014) ASTRO

Clinical Validation of RSI in RT-treated patients

Disease Site	N	Endpoint	Hazard Ratio Ref. Radioresistance	Clinical Outcome RS vs RR	p-value
Breast (Karolinska)	77	RFS	0.13 (0.02-1.0)	95% vs. 75% (5 yr)	0.02
Breast (Erasmus)	288	DMFS	0.57 (0.33-0.98)	77% vs. 64% (5 yr)	0.04
Breast (Curie,NKI	343	LRFS	0.23 (0.1, 0.531)	--	0.0006
Lung (Moffitt)	53	DFS	0.42 (0.25-0.92)	63% vs. 22% (5 yr)	0.02
Lung (Dir Chall)	27	DFS	0.44 (0.16, 1.18)	--	0.09
Lung (Korea)	16	DFS	0.27 (0.03, 2.17)	75% vs. 25% (5 yr)	0.18
GBM (TCGA)	214	OS	0.57 (0.38-0.85)	--	0.005
Pancreas* (Moffit)	49	OS	0.10 (0.02, 0.45)	78% vs. 42% vs. 8% (3 yr)	0.003
Prostate (Mayo)	82	DMFS	--	94% vs. 72% (10 yr)	0.03
Prostate (TJU)	132	BFFS	--	80% vs. 60% (5 yr)	0.026
Head and Neck (NKI)	92	LRFS	--	86% vs. 61% (2 yr)	0.05

But not in those without RT

Disease Site	N	Endpoint	Hazard Radio Ref. Radioresistance	Clinical Outcome RS vs RR	p Value
Breast (Karolinks)	82	RFS	1.21 (0.50-2.91)	77% vs. 71% (5 yr)	0.67
Breast (Erasmus)	62	DMFS	1.06 (0.23-4.83)	80% vs. 81% (5 yr)	0.94
Lung (Moffitt)	42	RFS	1.09 (0.45-2.65)	--	0.98
Lung (Dir Chall)	47	DFS	0.93 (0.50, 1.79)	19% vs. 14% (5 yr)	0.84
GBM (TCGA)	52	OS	--	5% vs. 5% (1 yr)	0.64
Pancreas (Moffitt)	31	OS	0.76 (0.29, 1.99)	69% vs. 67% (2 yr)	0.58
Prostate (Mayo)	536	DMFS	--	70% vs 71% (10 yr)	0.58

RSI

- RSI predicts outcome only in RT-treated patients.
- Site-agnostic
- Selected by NCI for further development through CADP.

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 33

The radiosensitivity index predicts for overall survival in glioblastoma

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Ahmed et al

- RSI as predictor of clinical outcome in GBM pts
  - TCGA data downloaded
  - Clinical and array based gene expression (Affymetrix HT Human Genome U133 Array Plate Set) level 2
- n = 270 patients identified
  - 214 RT and TMZ
  - 56 who did not undergo RT .
- RSI significant
  - OS on univariate and multivariate analyses
  - K-M OS @ 12 / 24 m:
    - 77.1% and 32.1% in quartile 4
    - 52.4% and 17.5% in quartile 1

Ahmed et al

- Sub-group analysis:
  - RSI is most predictive in *MGMT*-high patients.
- In GB patients with low *MGMT:*
  - age (p=0.03), PS (p<0.001) significant for OS
  - RSI (p=NS)
- RT dose escalation has not been proven beneficial in large trials of unstratified GB patients.
  - Perhaps explained by the smaller number of patients who could benefit from dose escalation being overwhelmed by the larger effect of *MGMT* promoter silencing and the radioresistant cadre of high-*MGMT* patients.

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ASTRO 2015

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Clinical Investigation

Differences Between Colon Cancer Primaries and Metastases Using a Molecular Assay for Tumor Radiation Sensitivity Suggest Implications for Potential Oligometastatic SBRT Patient Selection

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ASTRO 2015

- N=139 patients with primary colon cancer lesions + mets
  - Significant Δ RSI between primaries and mets
  - Significant Δ RSI between mets at different sites
    - Corresponds with LC after SBRT