Fattori predittivi e modellistica della risposta al trattamento

V. Valentini
Università Cattolica S.Cuore – Rome

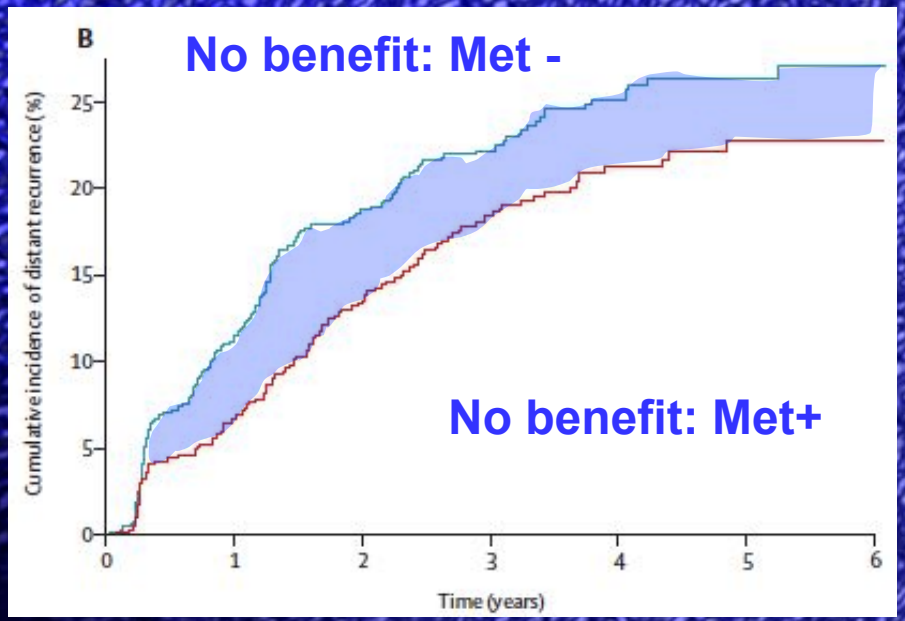
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli ART
Advanced Radiation Therapy

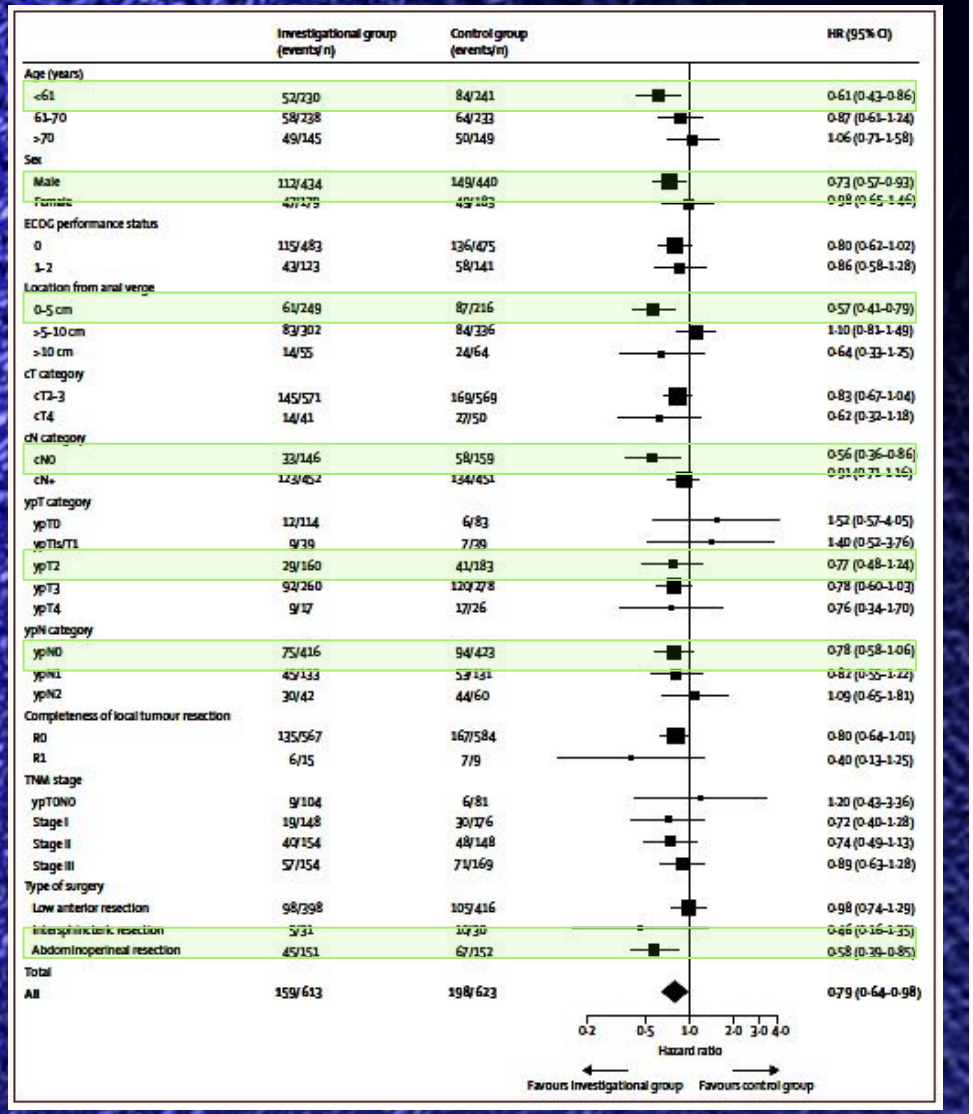
The issue of clinical decision

Gemelli ART
Advanced Radiation Therapy

Rodel C et Al – Lancet Oncol - 2015

Dealing with covariates





Gemelli ART
Advanced Radiation Therapy

Rodel C et Al – Lancet Oncol - 2015

Dealing with covariates

Logistic regression

Dataset: 400 cases

```
glm(formula = Outcome ~ Age + cT + cN, family = binomial(link = "logit"))

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.63606    0.63758  -5.703 1.18e-08 ***
Age           0.05229    0.00962   5.435 5.48e-08 ***
cT            0.27765    0.09908   2.802  0.00507 **
cN            0.62634    0.21899   2.860  0.00424 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

beta0 beta1 beta2 beta3

$$P = \frac{1}{1 + e^{-(\beta_0 + \beta_1 \cdot Age + \beta_2 \cdot cT + \beta_3 \cdot cN)}}$$

Gemelli ART
Advanced Radiation Therapy

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

Dealing with covariates

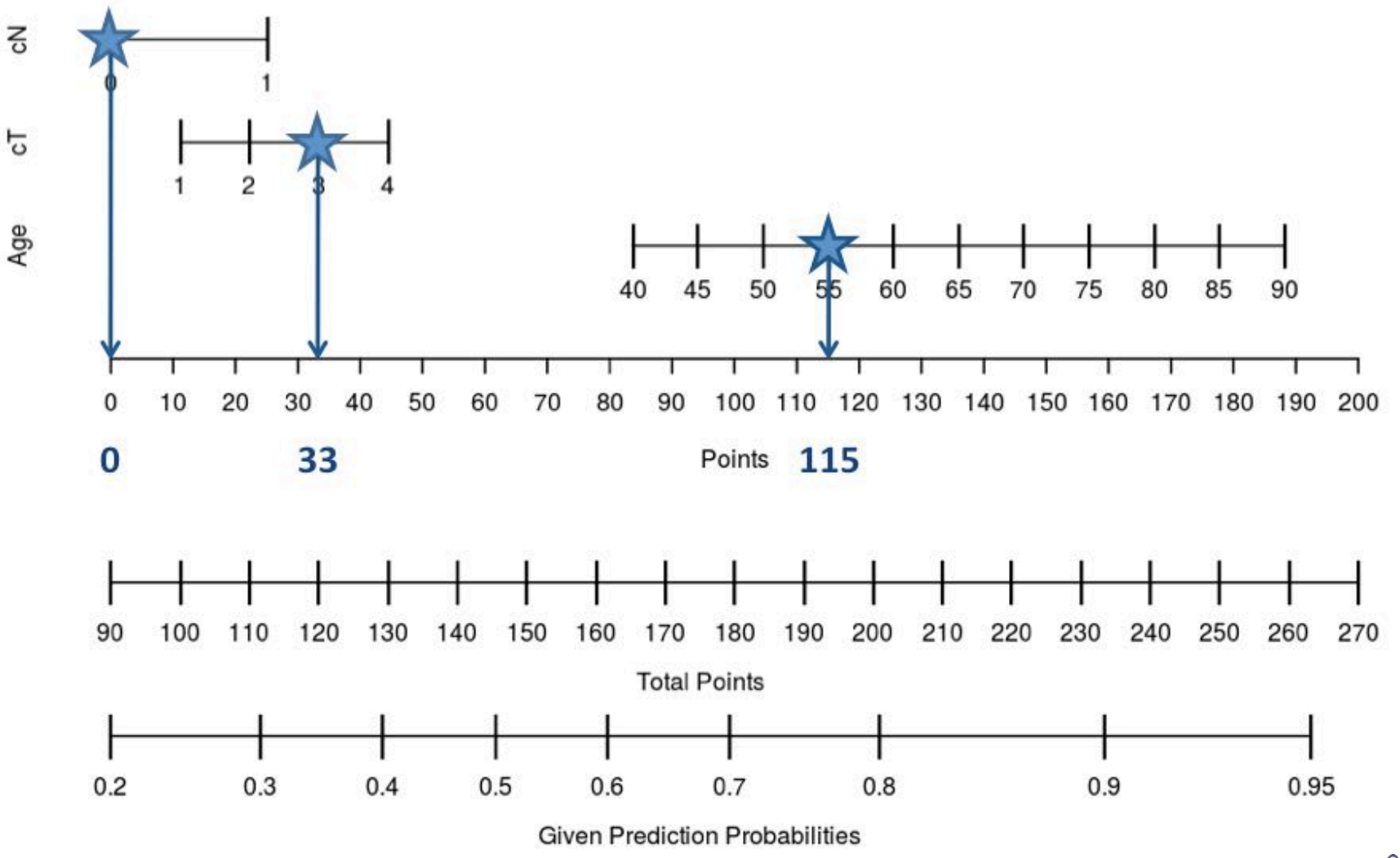
- By the model equation

$$P = \frac{1}{1 + e^{-(\beta_0 + \beta_1 \cdot Age + \beta_2 \cdot cT + \beta_3 \cdot cN)}}$$

How can I predict the probability for a patients with Age = 55, cT = 3, cN = 0 ?

$$P = \frac{1}{1 + e^{-(3.64 + 0.052 \cdot 55 + 0.28 \cdot 3 + 0.63 \cdot 0)}} = 0.518$$

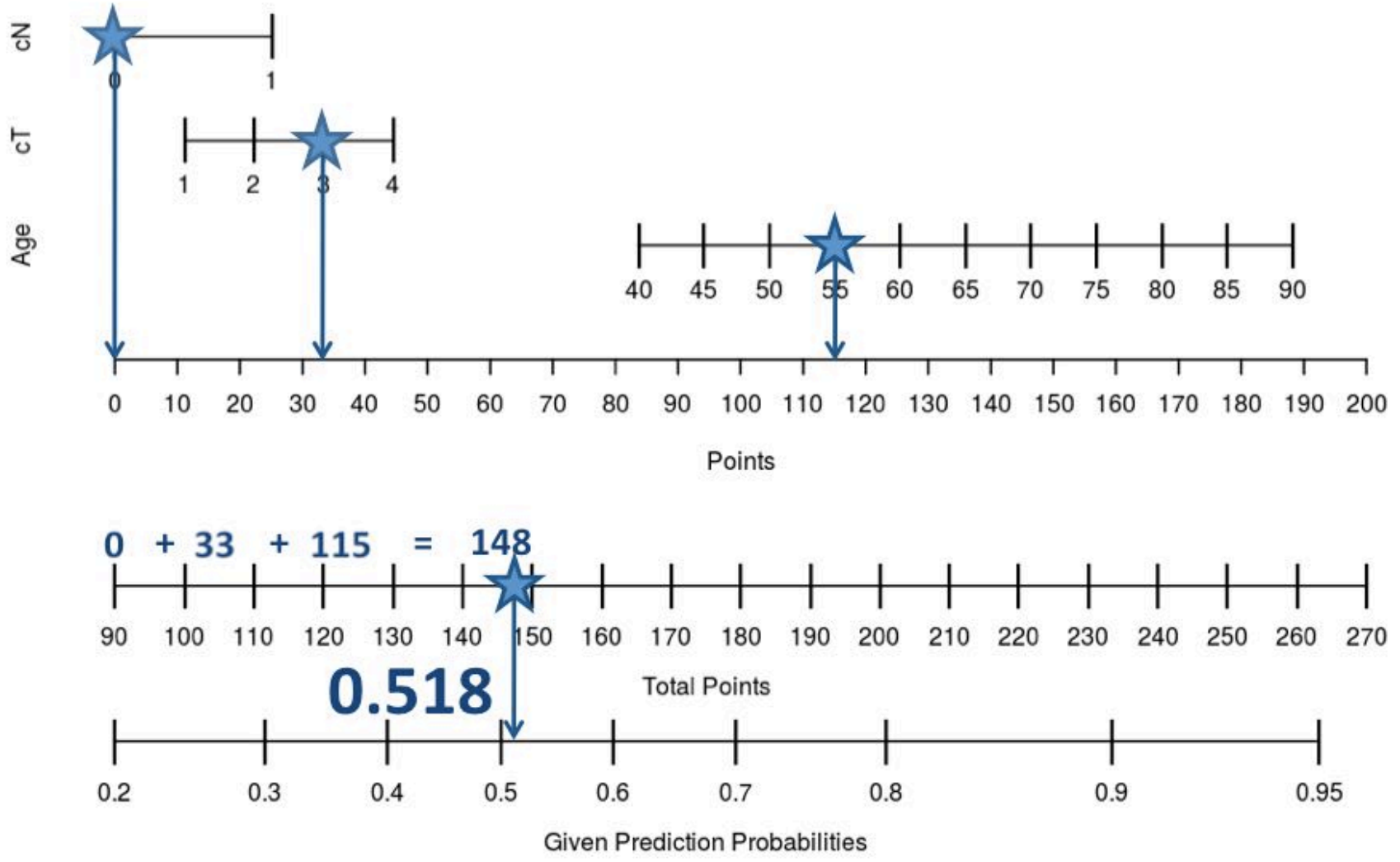
Dealing with covariates



Gemelli ART
Advanced Radiation Therapy

Datamining
Radiomics
KBO Labs
Knowledge Based Oncology Labs

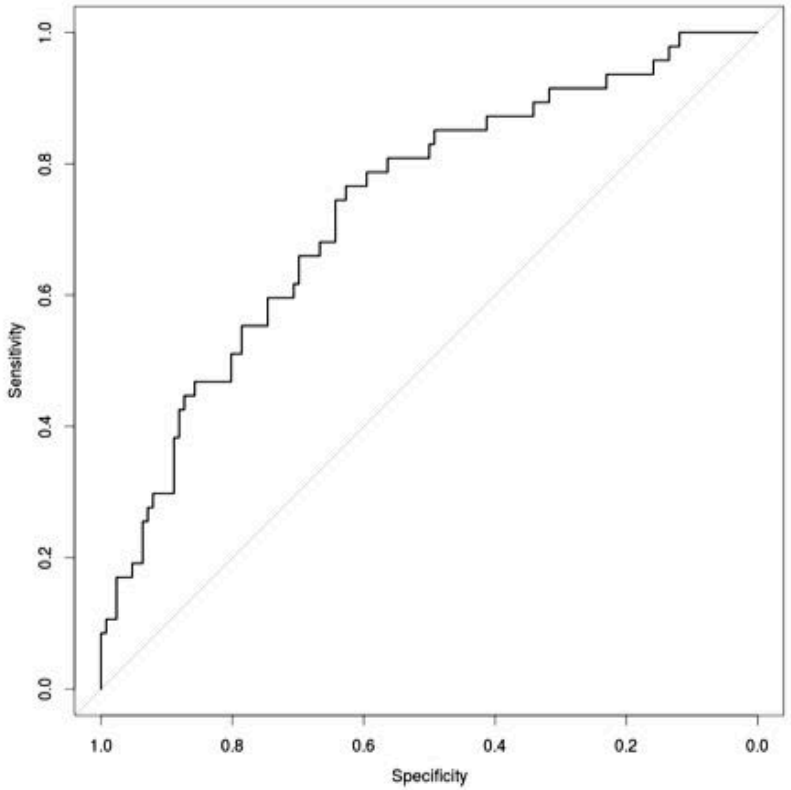
Dealing with covariates

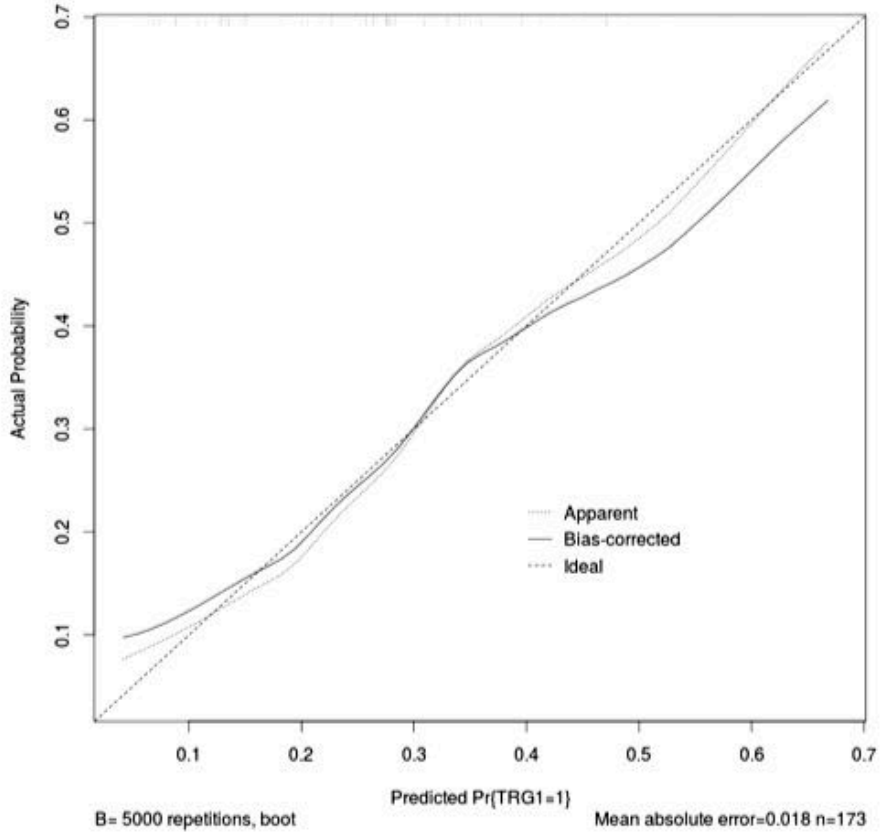


Gemelli ART
Advanced Radiation Therapy

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

Dealing with covariates





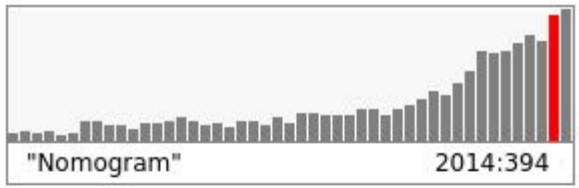
AUC = 0.73

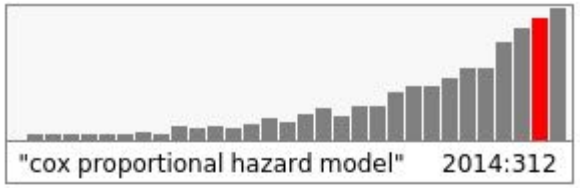
Bootstrap 5000 repetitions
Mean absolute error = 0.018

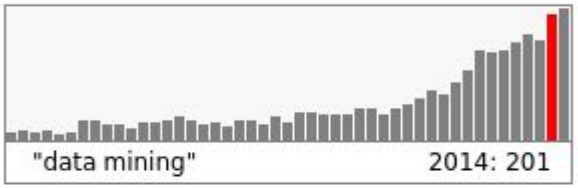
Gemelli ART
Advanced Radiation Therapy

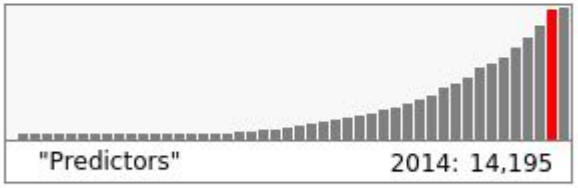
Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

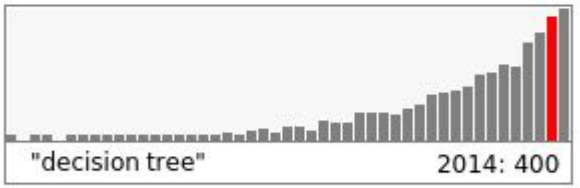
Personalization by prediction models

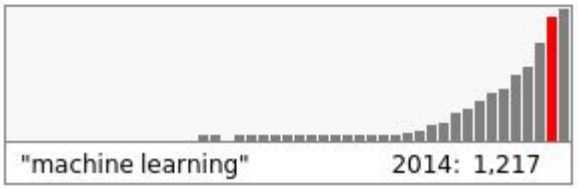


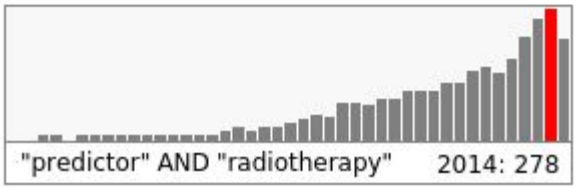












Gemelli ART
Advanced Radiation Therapy

Level of evidence scoring criteria

DIABETICMedicine

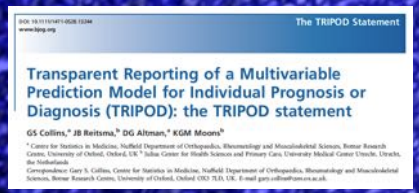
DOI: 10.1111/dme.12654

TRIPOD Statement

Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD Statement

G. S. Collins[1], J. B. Reitsma[2], D. G. Altman[1] and K. G. M. Moons[2]

[1]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK and [2]Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands



DOI: 10.1111/1471-0528.13244
www.bjog.org

The TRIPOD Statement

Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement

GS Collins,[a] JB Reitsma,[b] DG Altman,[a] KGM Moons[b]

[a] Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK; [b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

Correspondence: Gary S. Collins, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford OX3 7LD, UK. E-mail gary.collins@csm.ox.ac.uk

GUIDELINE

BJC

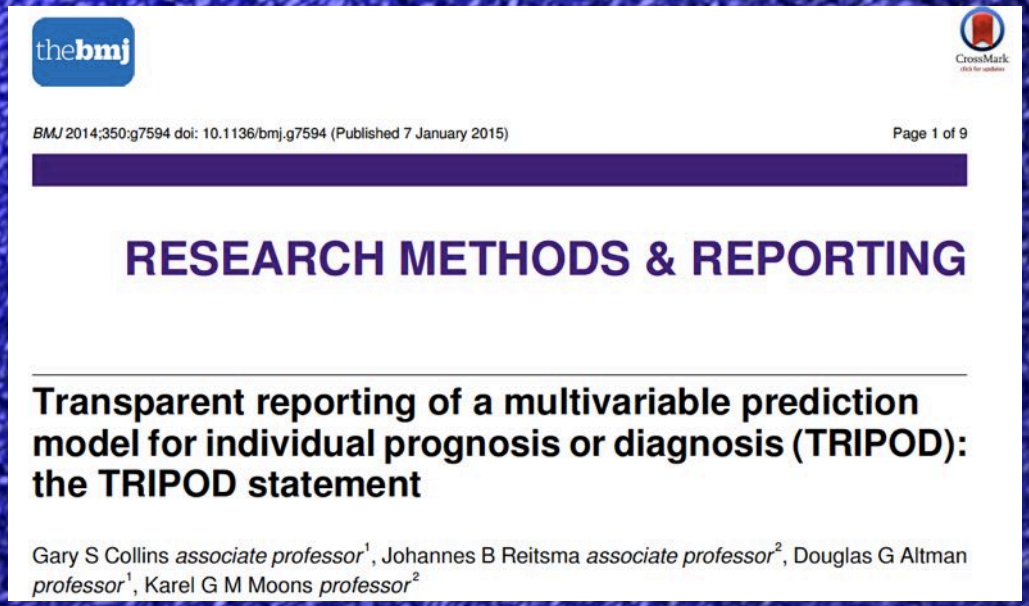
British Journal of Cancer (2015) 112, 251–259 | doi: 10.1038/bjc.2014.639

Keywords: prediction models; diagnostic; prognostic; model development; model validation; transparent reporting

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement

G S Collins*[,1], J B Reitsma[2], D G Altman[1] and K G M Moons[2]

[1]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford OX3 7LD, UK and [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, PO Box 85500, 3508GA Utrecht, The Netherlands



thebmj

CrossMark

BMJ 2014;350:g7594 doi: 10.1136/bmj.g7594 (Published 7 January 2015)

Page 1 of 9

RESEARCH METHODS & REPORTING

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement

Gary S Collins *associate professor*[1], Johannes B Reitsma *associate professor*[2], Douglas G Altman *professor*[1], Karel G M Moons *professor*[2]

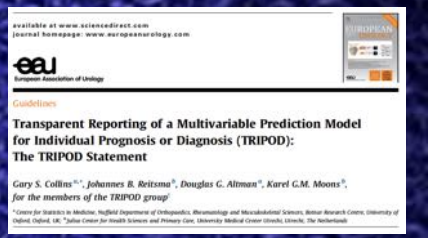
DOI: 10.1111/eci.12376

METHOD

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement

Gary S. Collins*,†,1, Johannes B. Reitsma‡,2, Douglas G. Altman*,†,1 and Karel G.M. Moons‡,2

*Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK, †Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands



available at www.sciencedirect.com
journal homepage: www.europeanurology.com

EUROPEAN

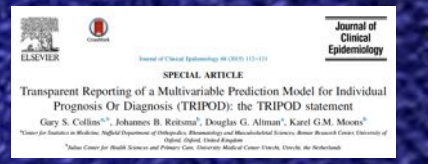
eau
European Association of Urology

Guidelines

Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): The TRIPOD Statement

Gary S. Collins[a,], Johannes B. Reitsma[b], Douglas G. Altman[a], Karel G.M. Moons[b], for the members of the TRIPOD group[†]*

[a] Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK; [b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands



ELSEVIER

Journal of Clinical Epidemiology

SPECIAL ARTICLE

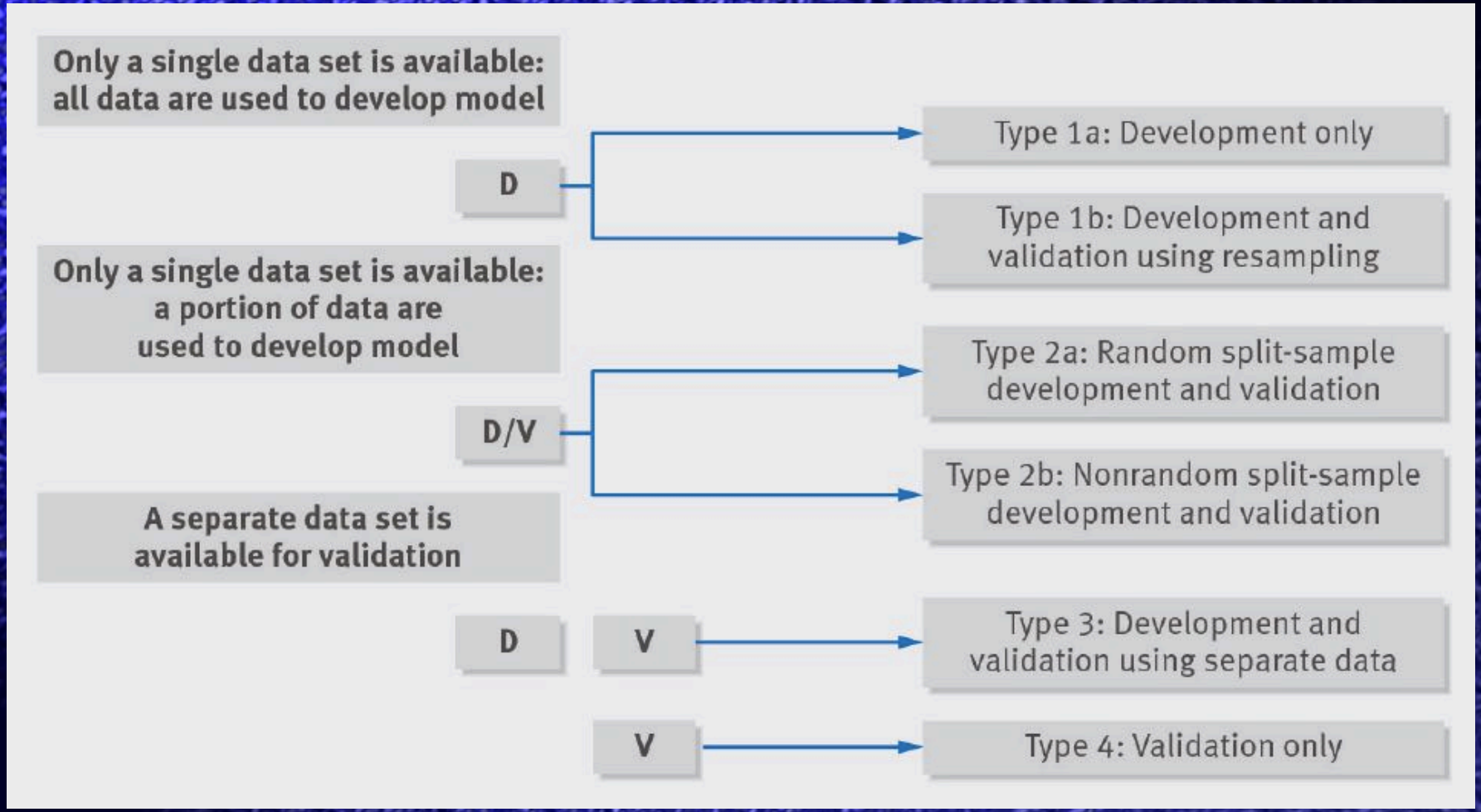
Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement

Gary S. Collins[a,*], Johannes B. Reitsma[b], Douglas G. Altman[a], Karel G.M. Moons[b]

[a]Centre for Statistics in Medicine, Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom

[b]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Level of evidence scoring criteria



Gemelli ART
Advanced Radiation Therapy

Collins GS et Al - *BMJ* – 2015

From Data Mining to Prediciton Model

- Clinical decision and covariates

- Prediction models in rectal cancer

- Transferability metric

Gemelli ART
Advanced Radiation Therapy

From Data Mining to Prediciton Model

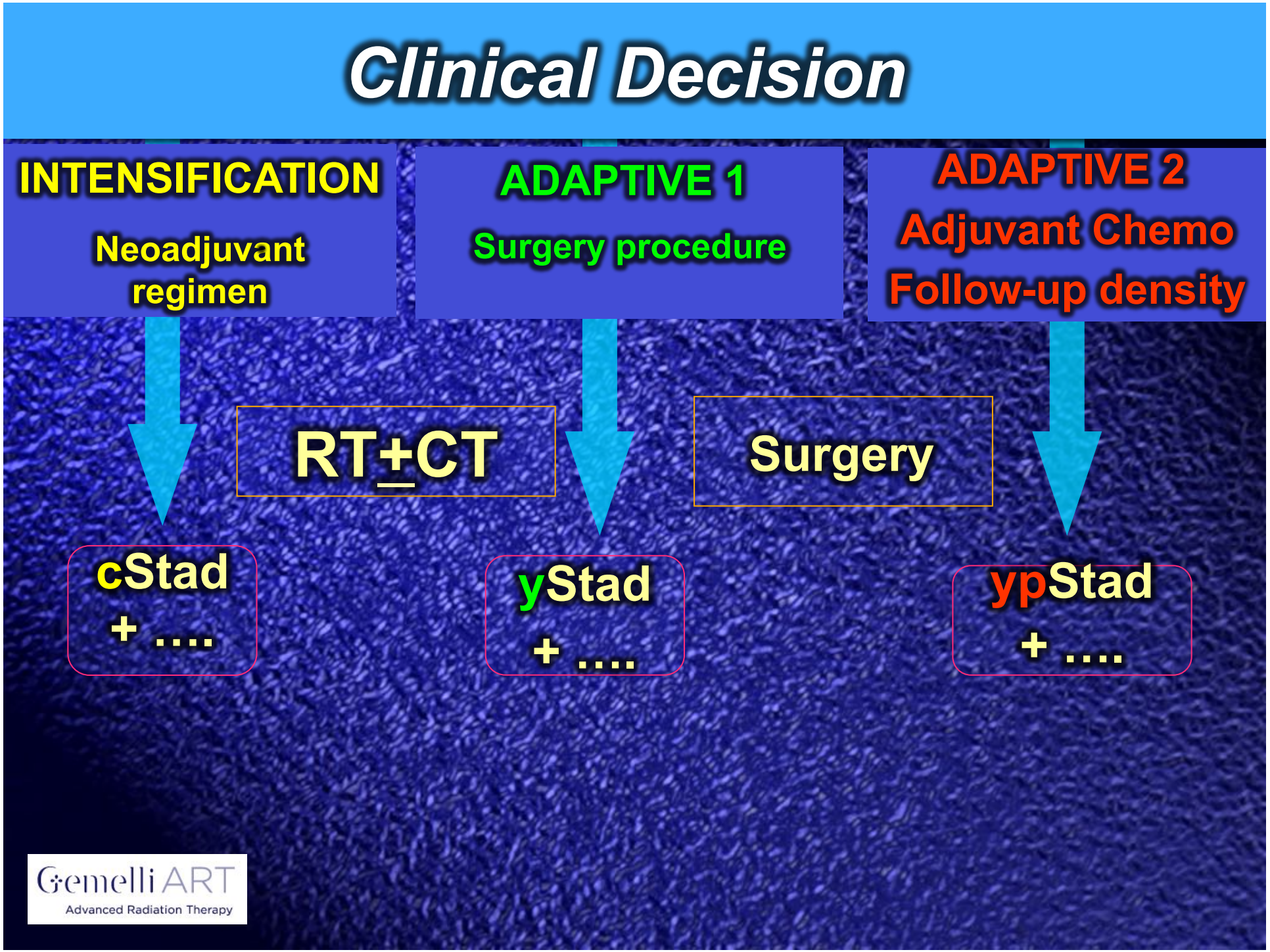
- Clinical decision and covariates

- Prediction models in rectal cancer

- Transferability metric

Gemelli ART
Advanced Radiation Therapy

Clinical Decision



Personalization by prediction models

3253 CRT patients

- The EORTC trial (Bosset et al, 2006)
- The French trial (Gerard et al. 2006)
- The German trial (Sauer et al. 2004)
- The Polish trial (Bujko et al. 2006)
- Italian CNR (Cionini L. et al. 2015)

Gemelli ART
Advanced Radiation Therapy

MAASTRO

Valentini V et Al - JCO - 2011

Personalization by prediction models

Variable	Cox Proportional Hazards Regression			Nomogram	
	HR*	95% CI	*P*	Performance (c-index)	95% CI
Local recurrences					
Sex	0.98	0.87 to 1.10	.703		
Age	0.87	0.78 to 0.97	.016†		
cT stage	1.18	1.06 to 1.31	.002†		
Tumor location	0.97	0.84 to 1.12	.644		
RT dose	0.98	0.85 to 1.12	.732	Training: 0.71	0.67 to 0.74
Concurrent chemotherapy	0.81	0.72 to 0.91	.001†	Validation: 0.68	0.59 to 0.76
Surgery procedure	1.15	1.00 to 1.33	.057		
pT stage	1.64	1.38 to 1.95	< .001†		
pN stage	1.26	1.13 to 1.40	< .001†		
Adjuvant chemotherapy	0.81	0.72 to 0.92	.001†		
Distant metastases					
Sex	0.94	0.87 to 1.01	.100		
Age	1.00	0.93 to 1.08	.941		
cT stage	0.99	0.91 to 1.06	.723		
Tumor location	0.92	0.84 to 1.00	.062		
RT dose	0.95	0.88 to 1.03	.193	Training: 0.71	0.69 to 0.74
Concurrent chemotherapy	1.05	0.97 to 1.13	.238	Validation: 0.73	0.68 to 0.77
Surgery procedure	1.12	1.03 to 1.23	.010†		
pT stage	1.42	1.28 to 1.57	< .001†		
pN stage	1.54	1.44 to 1.64	< .001†		
Adjuvant chemotherapy	0.90	0.83 to 0.97	.006†		
Overall survival					
Sex	0.87	0.81 to 0.94	.001†		
Age	1.13	1.05 to 1.22	.001†		
cT stage	1.13	1.06 to 1.21	< .001†		
Tumor location	0.98	0.90 to 1.07	.710		
RT dose	0.91	0.85 to 0.98	.016†	Training: 0.68	0.66 to 0.71
Concurrent chemotherapy	1.04	0.97 to 1.12	.302	Validation: 0.70	0.65 to 0.74
Surgery procedure	1.18	1.08 to 1.28	< .001†		
pT stage	1.33	1.21 to 1.46	< .001†		
pN stage	1.35	1.26 to 1.44	< .001†		
Adjuvant chemotherapy	0.82	0.76 to 0.88	< .001†		

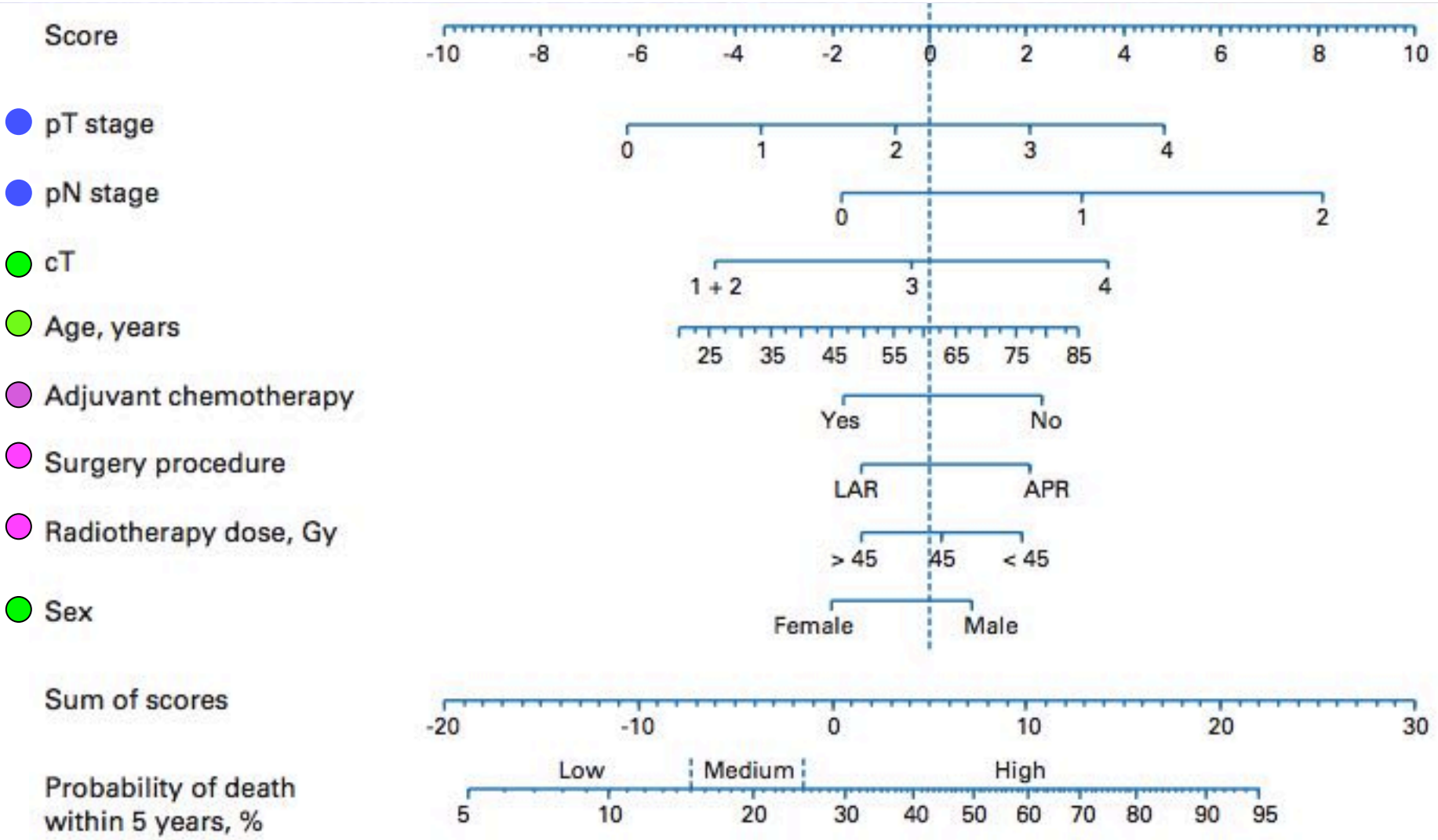
Gemelli ART
Advanced Radiation Therapy

MAASTRO

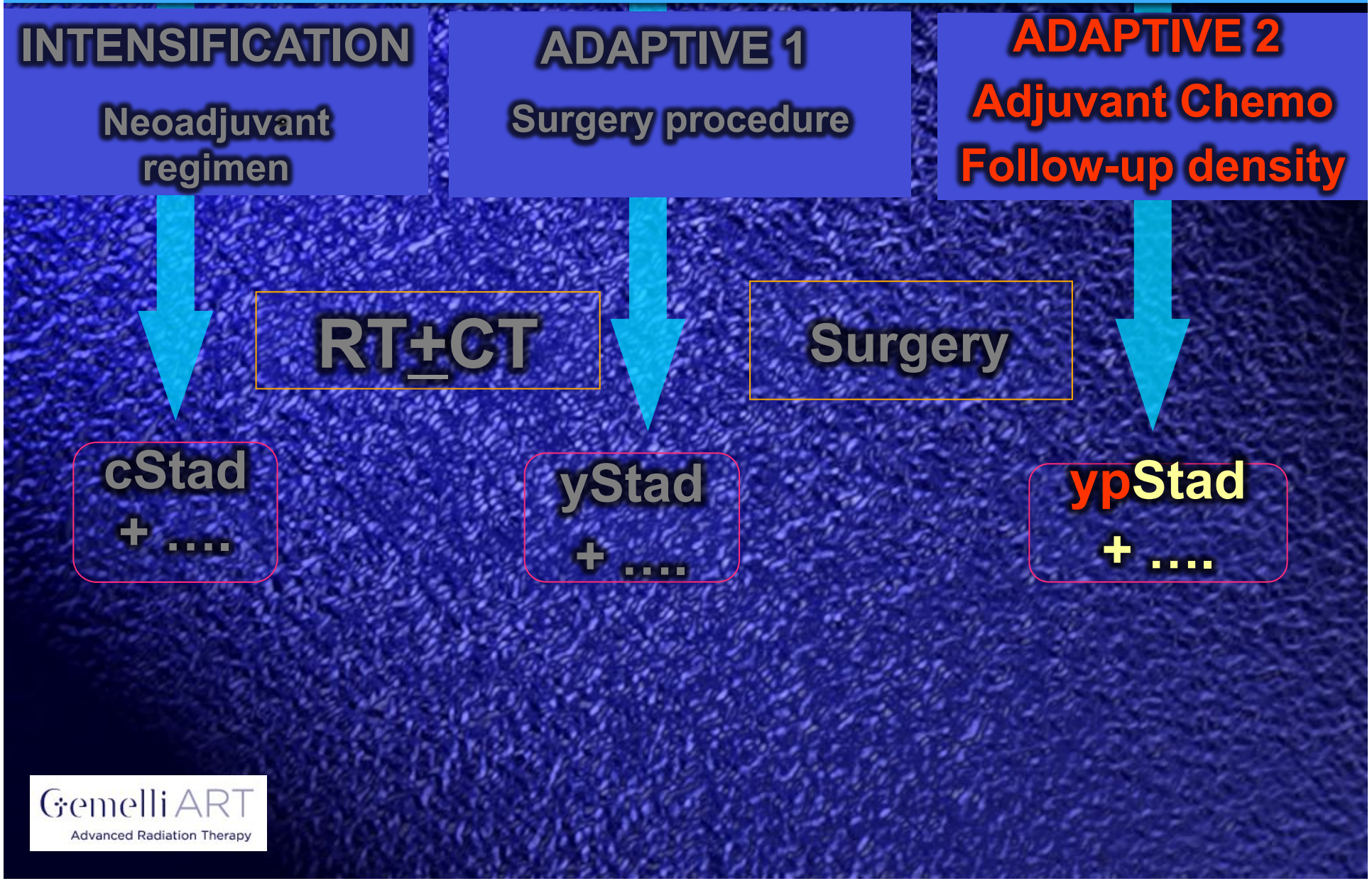
Valentini V et Al - JCO - 2011

Nomogram

Survival



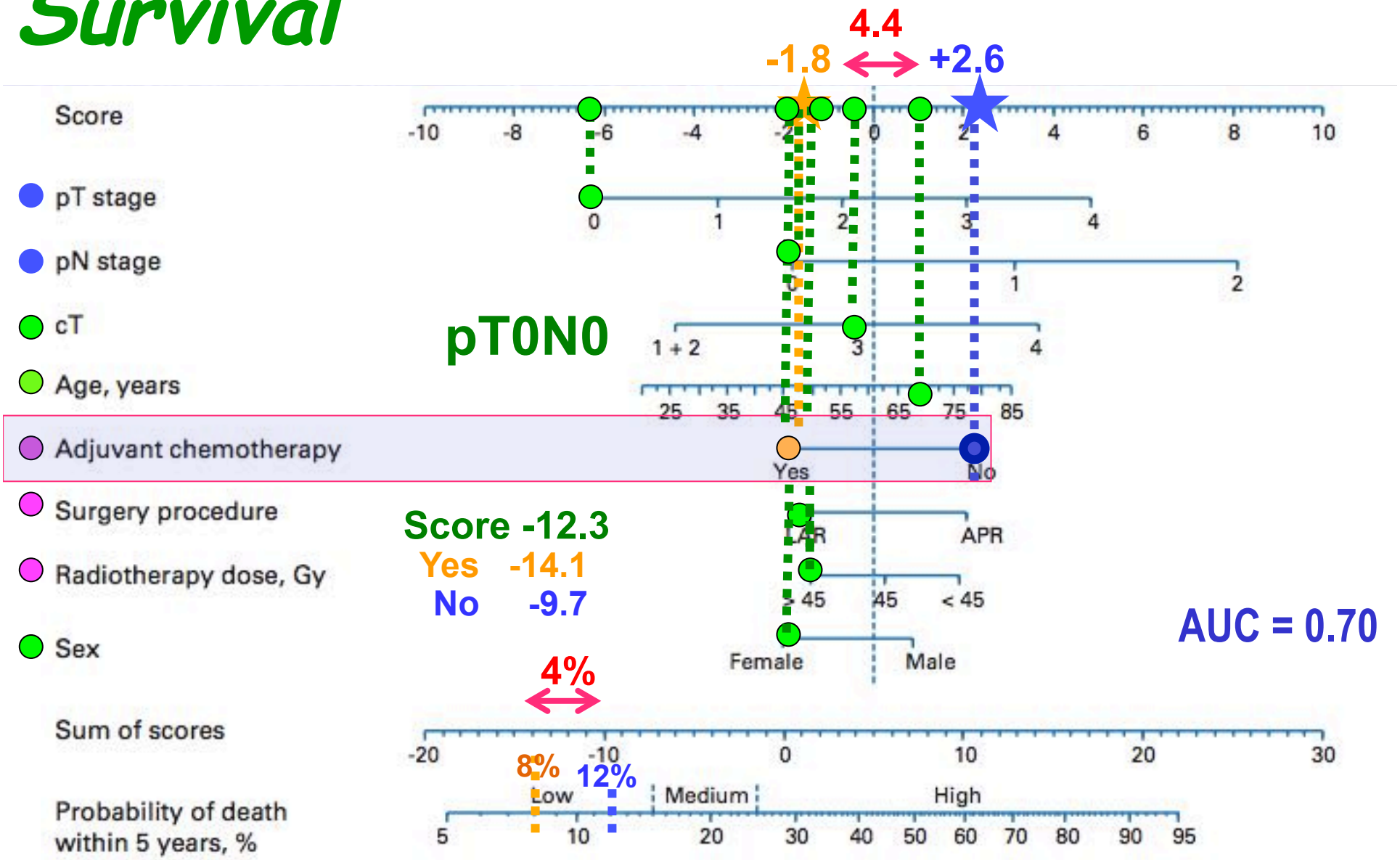
Clinical Decision



Gemelli ART
Advanced Radiation Therapy

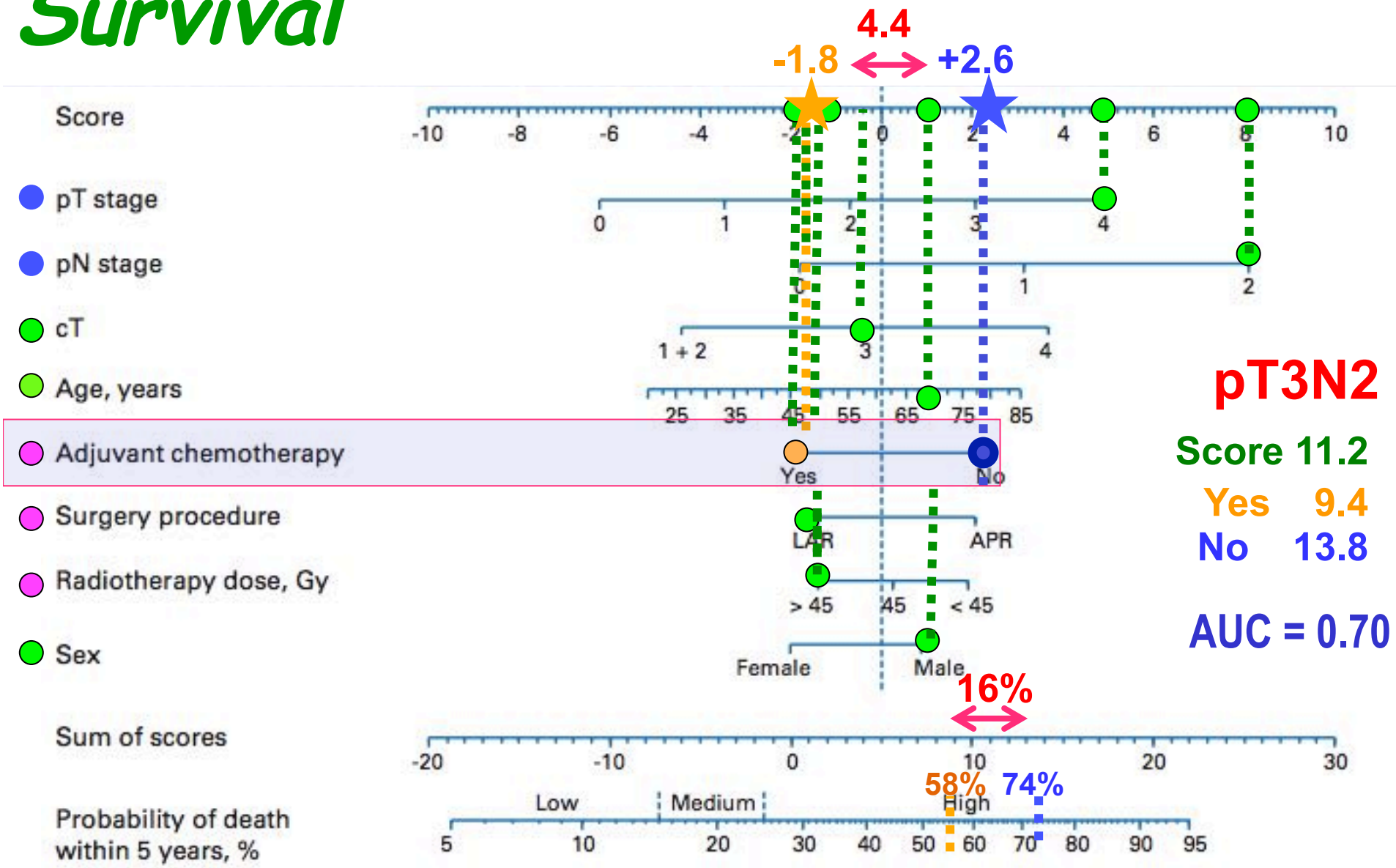
Nomogram

Survival



Nomogram

Survival



Support to Clinical Decision

INTENSIFICATION

Neoadjuvant regimen

ADAPTIVE 1

Surgery procedure

ADPTIVE 2

Adjuvant Chemo

Follow-up density

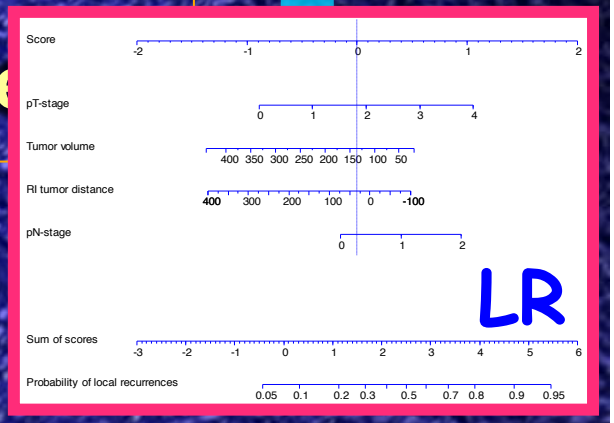
RT±CT

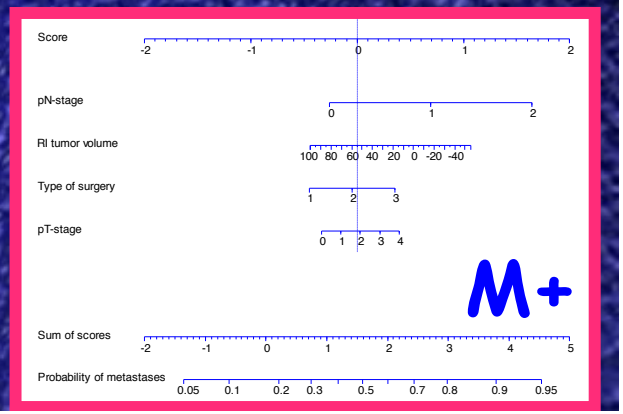
Surg

cStad

yStad

PET

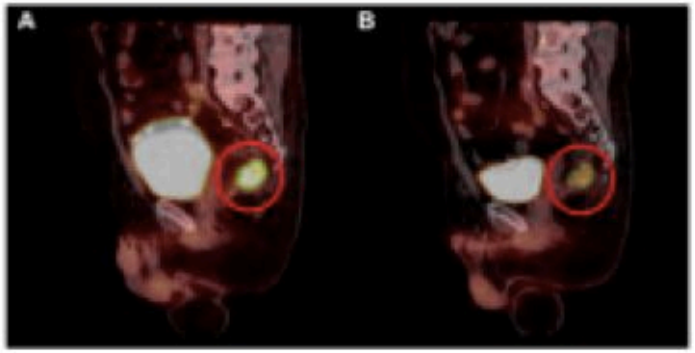




Personalization by prediction models

Leuven Maastricht Rome Rovigo

Pre-CRT no PET	Pre-CRT with PET	During CRT with PET	Post-CRT with PET
Age Gender BMI WHO cT-stage cN-stage Tumor length Tumor location	GTV Max.Diam. SUV_{min} SUV_{mean} SUV_{max} SUV_{std} $Size_{X,Y,Z}$	RI GTV RI Max.Diam. RI SUV_{mean} RI SUV_{max}	RI GTV RI Max.Diam. RI SUV_{mean} RI SUV_{max}



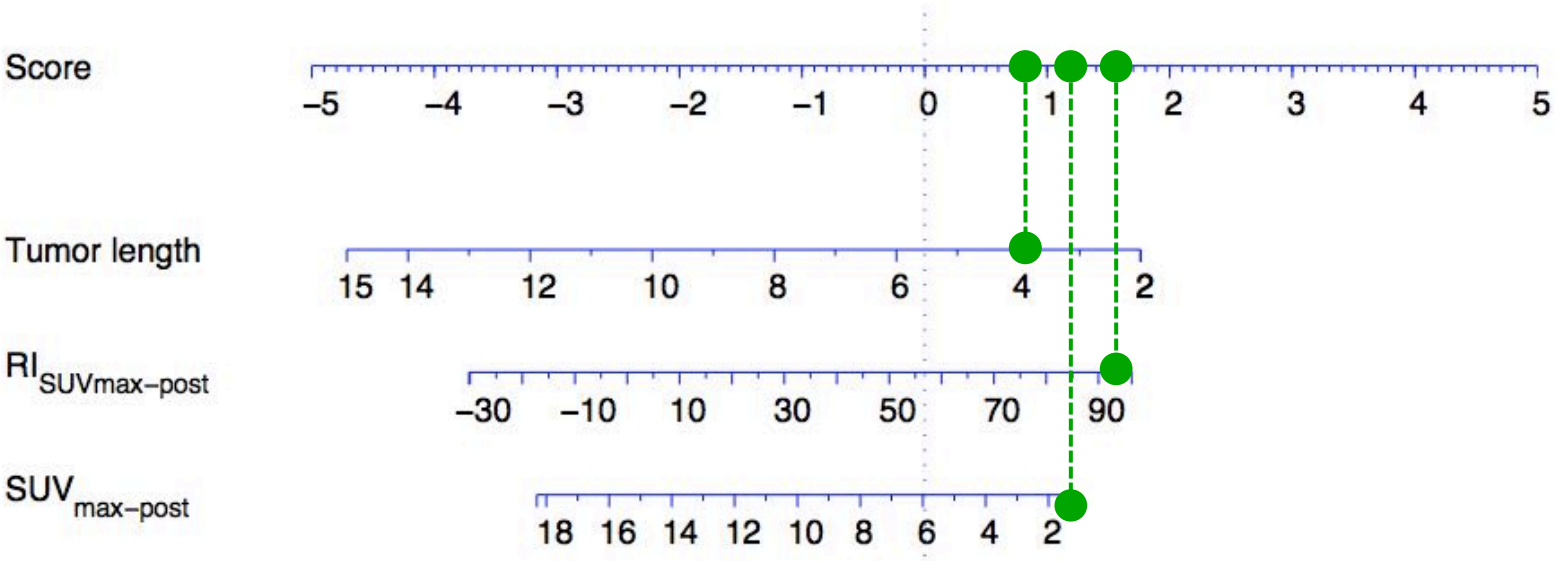
Gemelli ART
Advanced Radiation Therapy

MAASTRO

Van Stiphout R, Valentini V et Al – Radioth Oncol - 2011

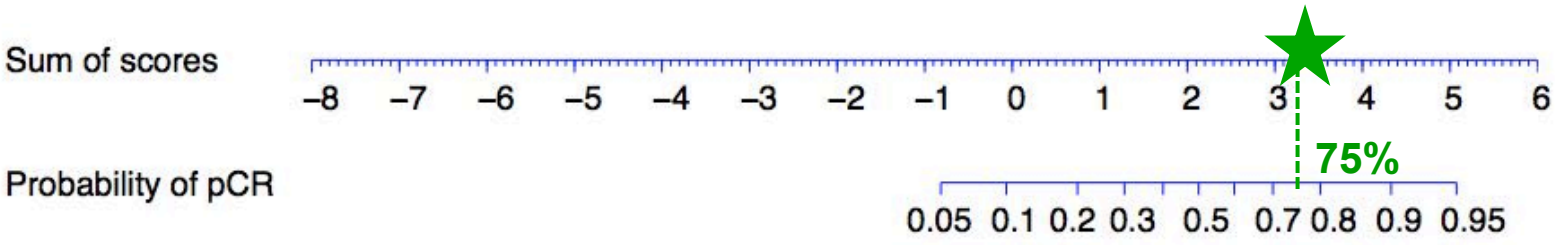
Nomogram

pCR



Sum of scores 3.3

AUC = 0.86



Van Stiphout R, Valentini V et Al – Radioth Oncol - 2011

Support to Clinical Decision

INTENSIFICATION

Neoadjuvant regimen

ADAPTIVE 1

Surgery procedure

ADPTIVE 2

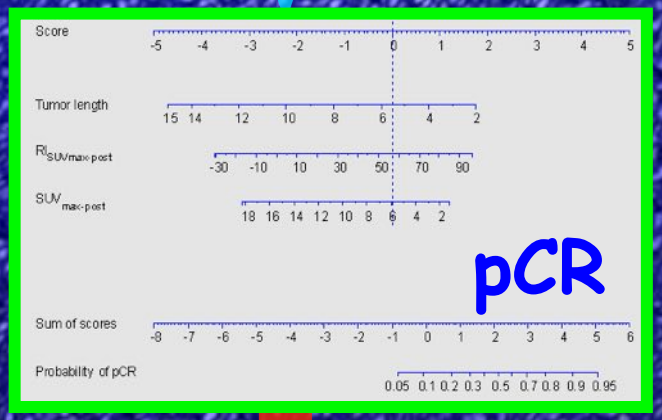
Adjuvant Chemo

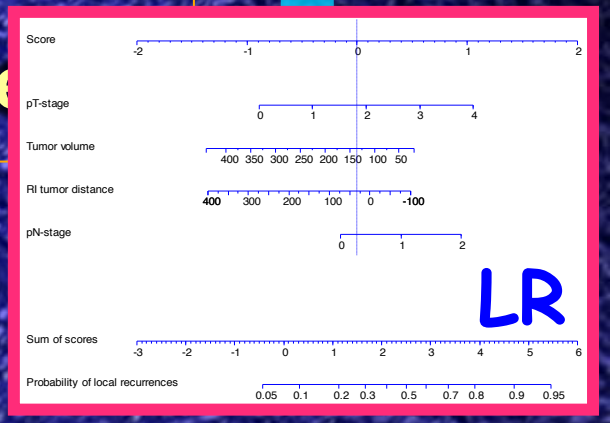
Follow-up density

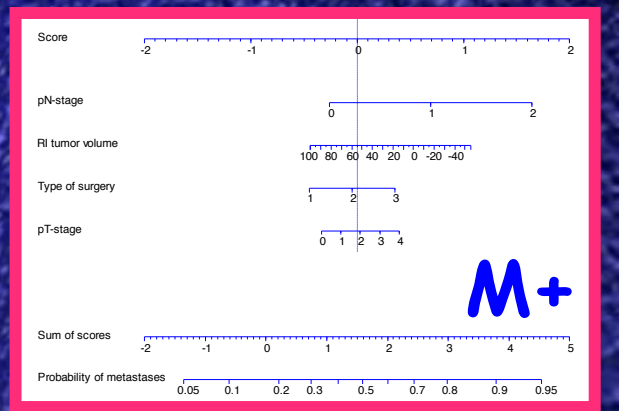
RT±CT

Surg

cStad







PET

Thunder Trial

Study characteristics

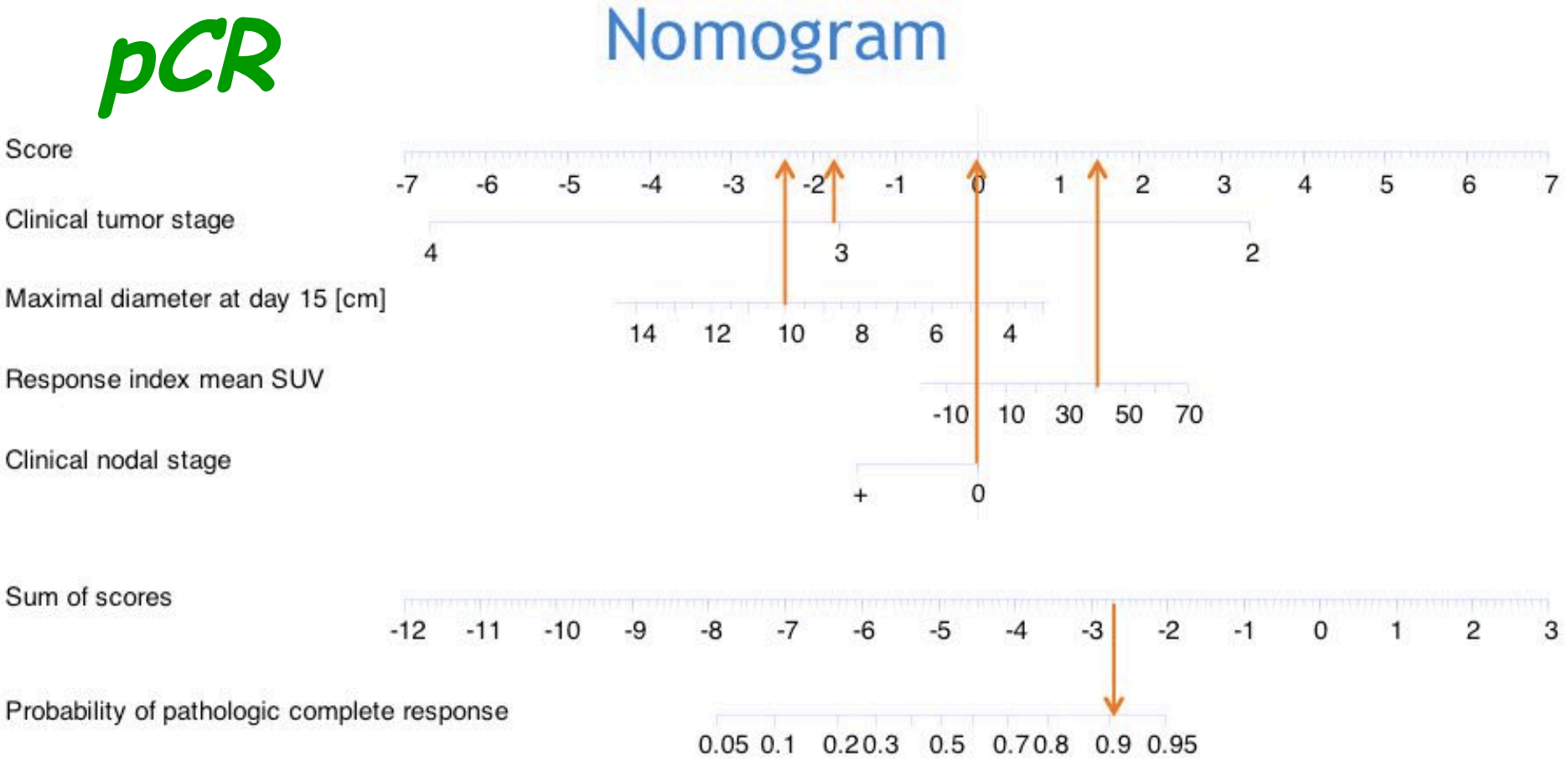
	Maastricht [Training]	Rome [Validation]
THUNDER 2010 - 2012	65	59
Prospective studies 2004 - 2009	47	19
Total	112	78

Pretreatment	During treatment	Outcome
Gender Age cT-stage cN-stage	SUVmean15 SUVmax15 MTV15 MaxDiam15	pCR based on ypT0N0
SUVmean0 SUVmax0 MTV0 MaxDiam0	RI_SUVmean RI_SUVmax RI_MTV RI_MaxDiam	

van Stiphout R et Al - Radiot Oncol - 2014

Rectal Cancer perspective: IGTherapy

pCR



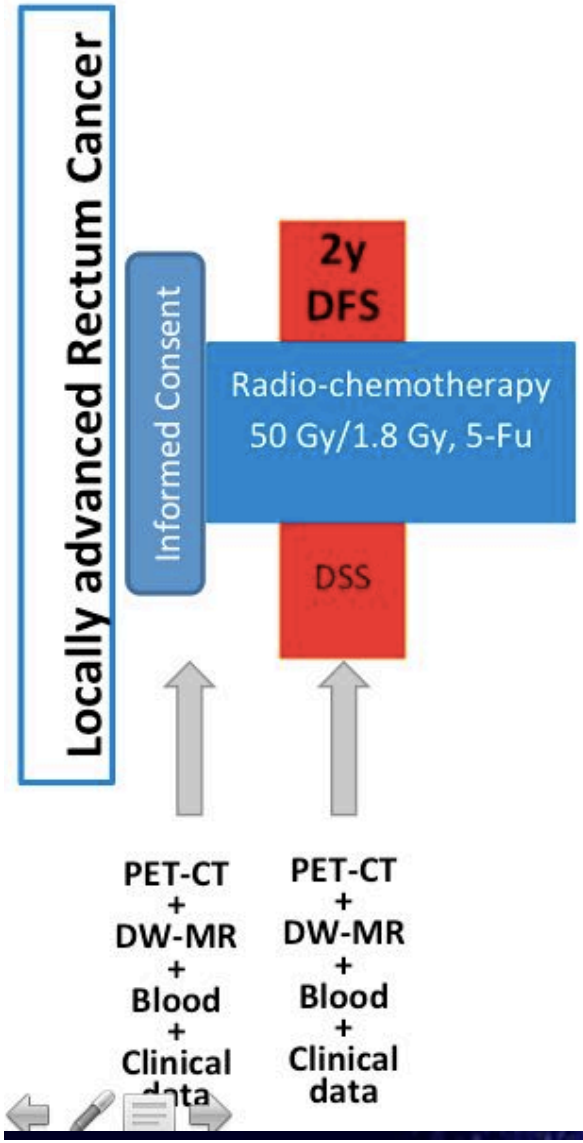
Gemelli ART
Advanced Radiation Therapy

MAASTRO

Van Stiphout R et Al – ESTRO Forum - 2013

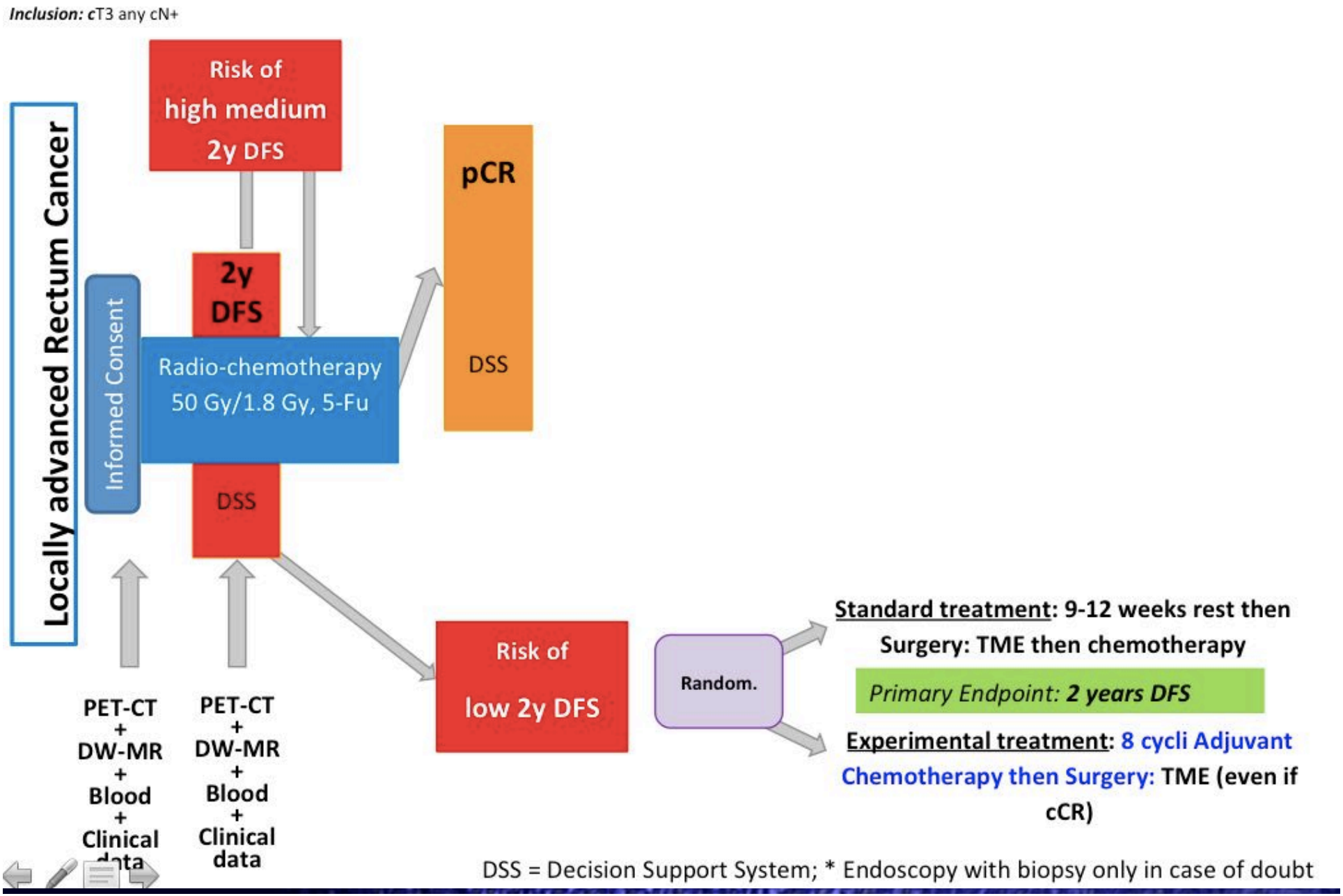
THUNDER-2 Trial Framework

Inclusion: *c*T3 any cN+

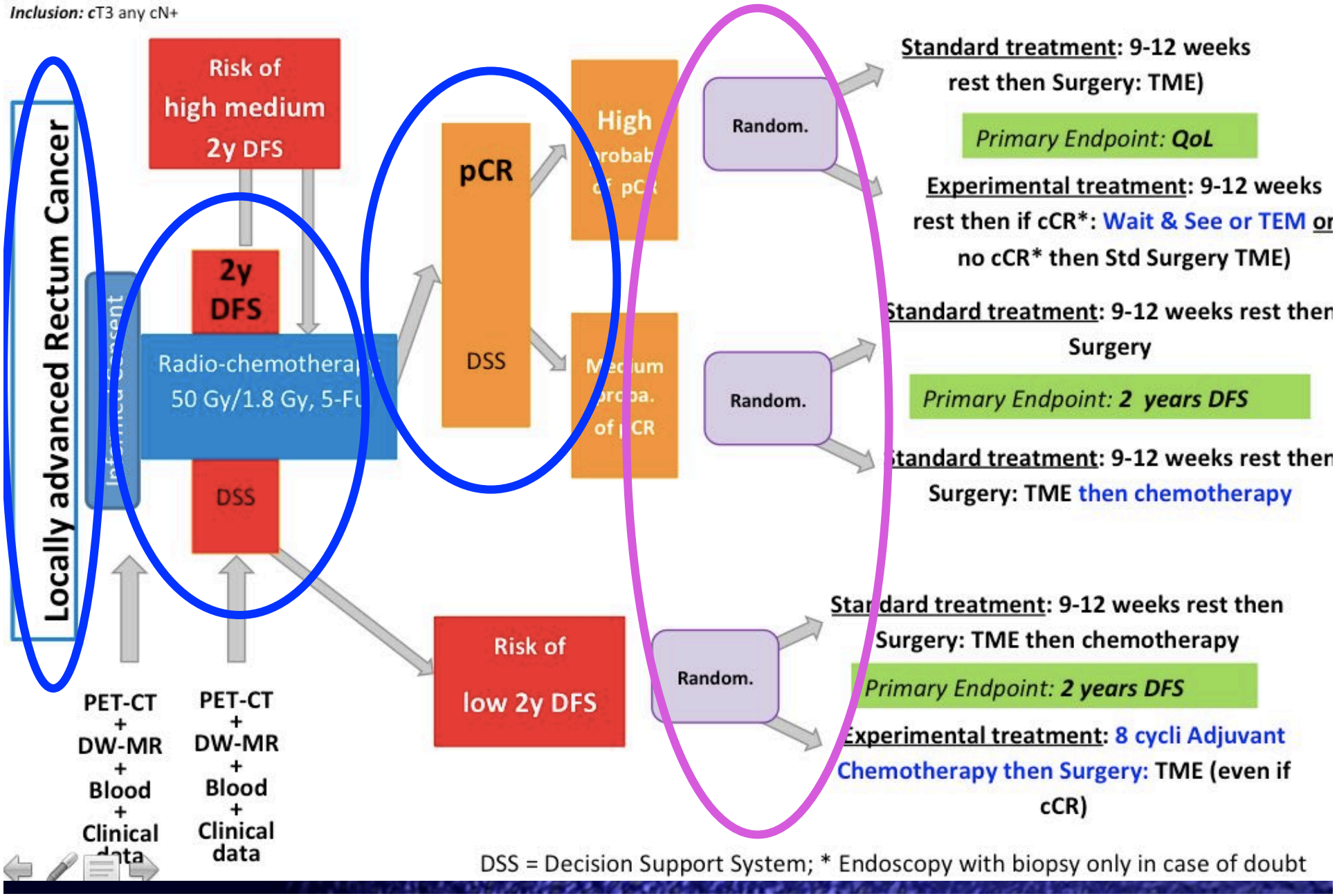


DSS = Decision Support System; * Endoscopy with biopsy only in case of doubt

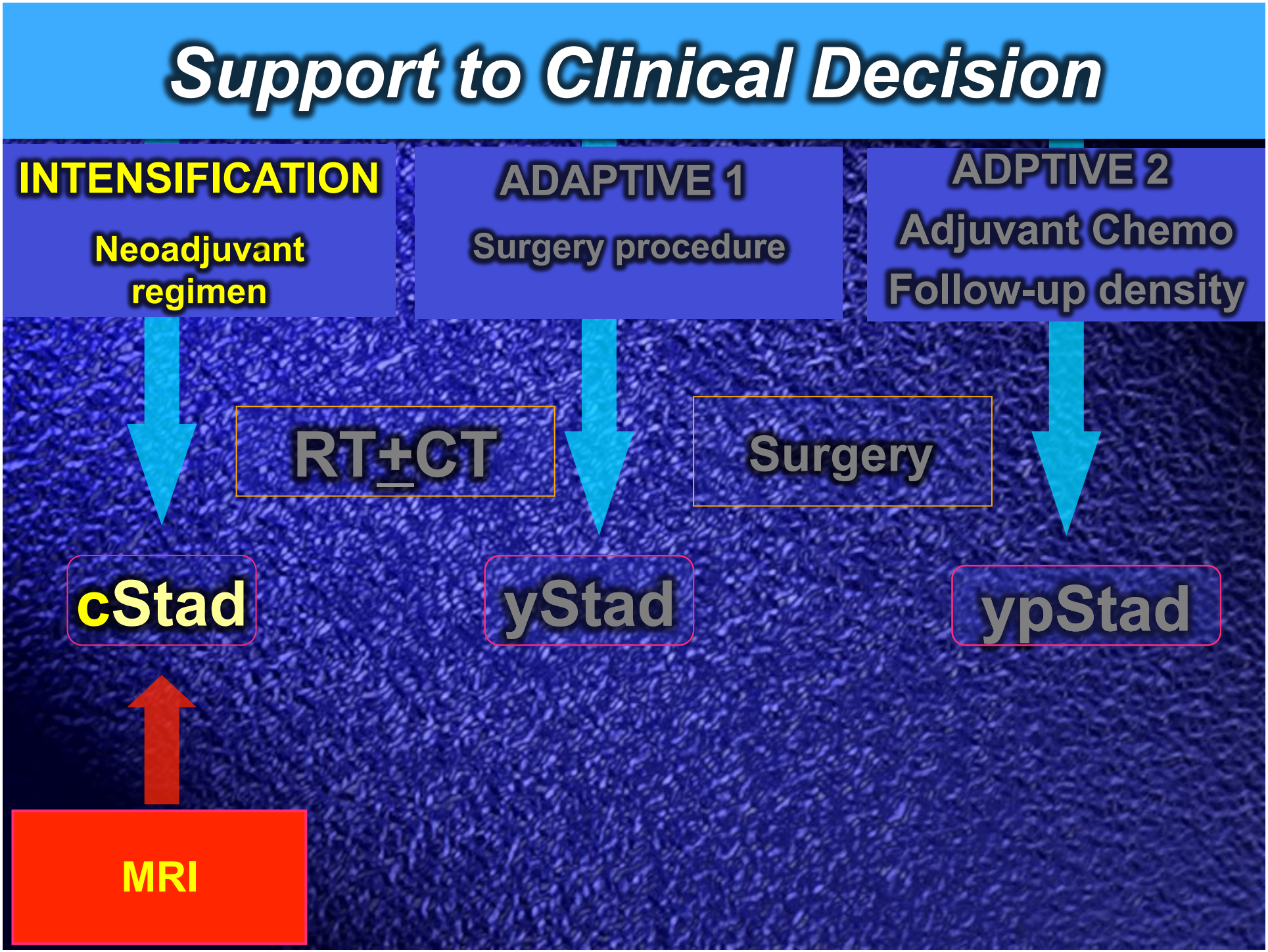
THUNDER-2 Trial Framework



THUNDER-2 Trial Framework

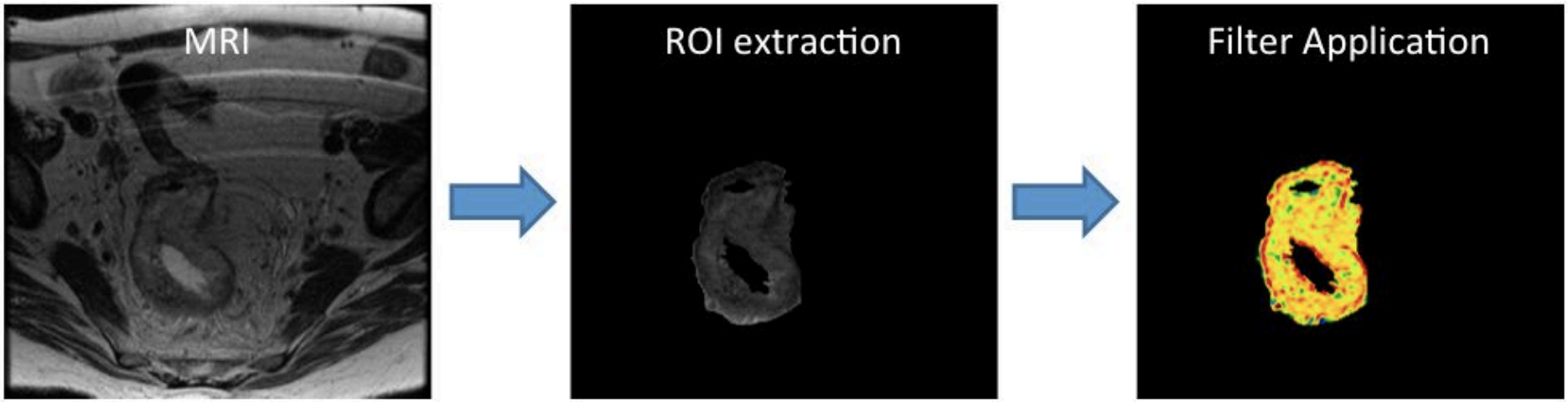


Support to Clinical Decision



Personalization by prediction models

Pre-process RAW signal for enhancing **tumor texture**



Gemelli ART
Advanced Radiation Therapy

Datamining
Radiomics
KBO Labs
Knowledge Based Oncology Labs

Personalization by prediction models

Multivariate analysis by logistic regression with following entry variables:

1) cT
2) cN
3) GTV Volume
4) GTV Surface
5) Equivalent Sphere Volume / GTV Surface
6) Entropy $\sigma = 0.49$
7) Skewness $\sigma = 0.69$

Final model:

DATA SET: 176 patients

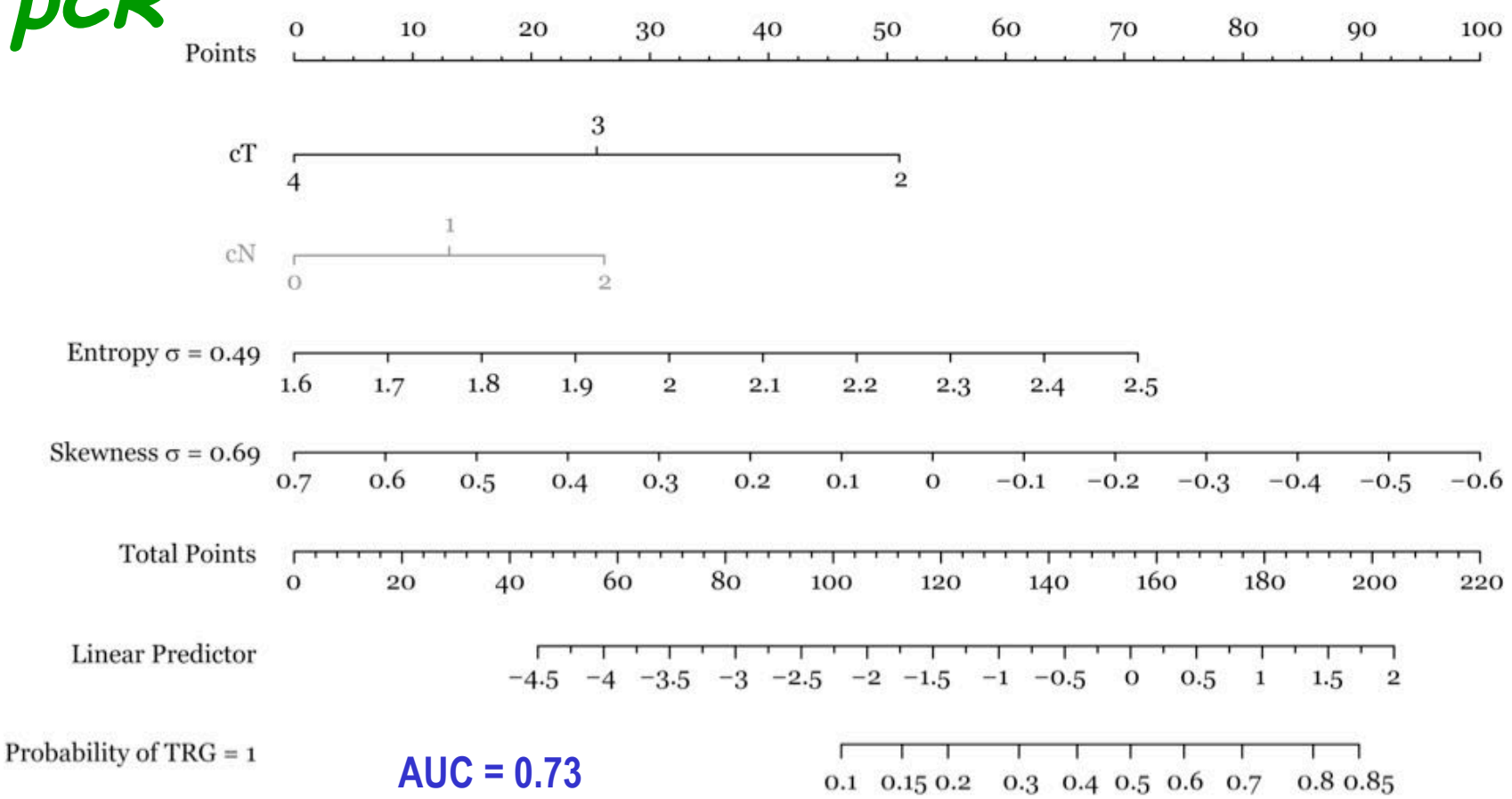
```
Coefficients:
                  Estimate Std. Error z value Pr(>|z|)
(Intercept)       -5.1466     3.9229  -1.312  0.18954
cT                -1.0442     0.3584  -2.913  0.00358 **
cN                 0.5350     0.3412   1.568  0.11689
Entr.Sigma.0.49    3.2354     1.6420   1.970  0.04880 *
Skew.Sigma.0.69   -3.1480     1.1601  -2.714  0.00666 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Gemelli ART
Advanced Radiation Therapy

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

Personalization by prediction models

pCR



AUC = 0.73

Gemelli ART
Advanced Radiation Therapy

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

Support to Clinical Decision

INTENSIFICATION

Neoadjuvant regimen

ADAPTIVE 1

Surgery procedure

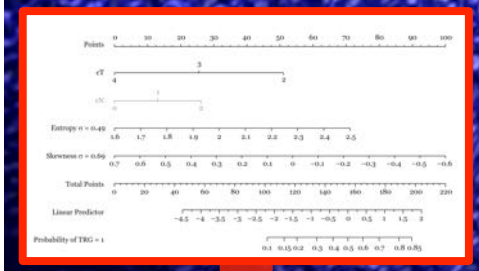
ADPTIVE 2

Adjuvant Chemo

Follow-up density

RT±CT

Surgery



yStad

ypStad

MRI

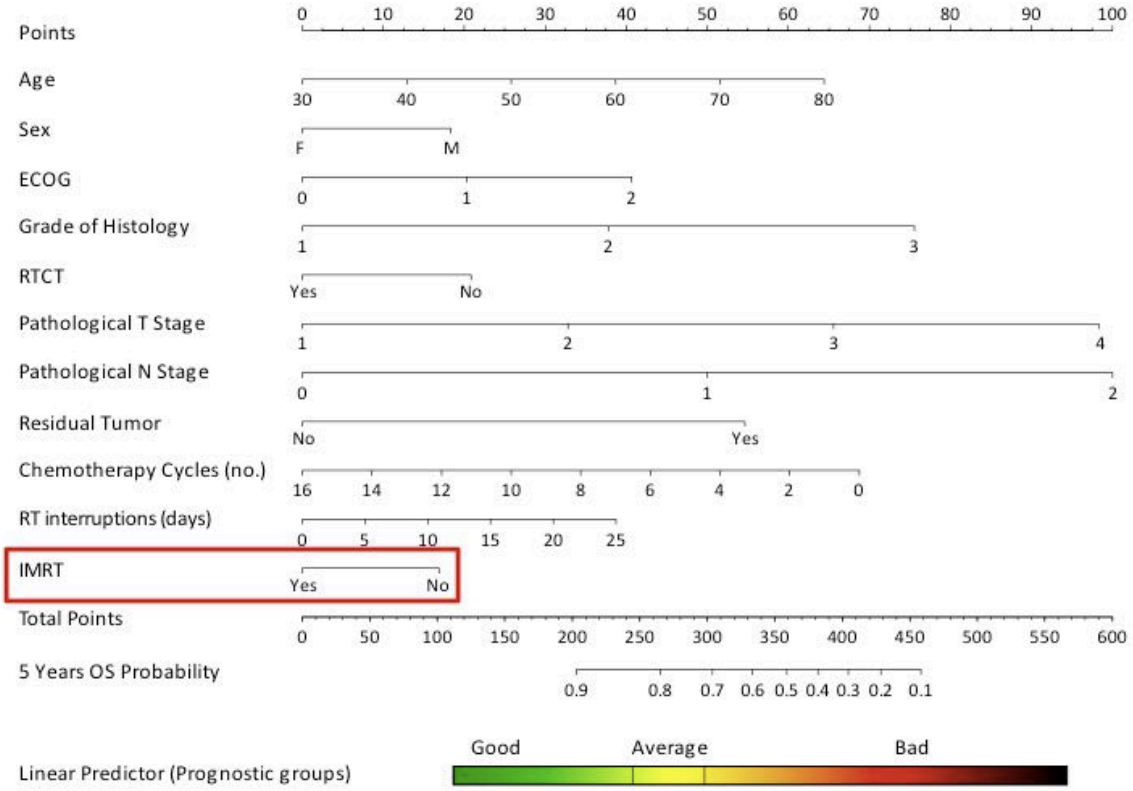
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli ART
Advanced Radiation Therapy

Postoperative RT in rectal cancer

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

- Cancer Institute Beijing 1798 pts



Gemelli ART
Advanced Radiation Therapy

Liu W et Al - *ASTRO* – 2014

Personalization by prediction models

	Age	Sex	ECOG	Grade	RTCT	pT	pN	Residual tumor	CT cycles	RT stop days	IMRT	Pearson Test
Age	1,00	0,07	0,09	-0,07	-0,11	-0,05	-0,09	-0,02	**-0,21**	0,00	-0,02	-1,00
Sex	0,07	1,00	0,02	-0,01	0,00	0,02	-0,04	0,01	0,01	-0,03	0,04	-0,80
ECOG	0,09	0,02	1,00	0,05	-0,03	0,05	0,04	0,04	-0,08	0,07	0,06	-0,60
Grade	-0,07	-0,01	0,05	1,00	0,04	0,05	**0,29**	0,14	0,06	-0,01	0,07	-0,40
RTCT	-0,11	0,00	-0,03	0,04	1,00	0,05	0,07	-0,01	0,11	-0,01	0,18	-0,20
pT	-0,05	0,02	0,05	0,05	0,05	1,00	0,01	0,13	0,06	0,01	0,04	0,00
pN	-0,09	-0,04	0,04	**0,29**	0,07	0,01	1,00	0,14	**0,28**	0,01	0,06	0,20
Residual tumor	-0,02	0,01	0,04	0,14	-0,01	0,13	0,14	1,00	0,04	0,01	0,01	0,40
CT cycles	**-0,21**	0,01	-0,08	0,06	0,11	0,06	**0,28**	0,04	1,00	-0,01	0,11	0,60
RT stop days	0,00	-0,03	0,07	-0,01	-0,01	0,01	0,01	0,01	-0,01	1,00	0,02	0,80
IMRT	-0,02	0,04	0,06	0,07	0,18	0,04	0,06	0,01	0,11	0,02	1,00	1,00

Sig. level > 0.2: no significant correlation among IMRT and other covariates

Gemelli ART
Advanced Radiation Therapy

Liu W et Al - *ASTRO* – 2014

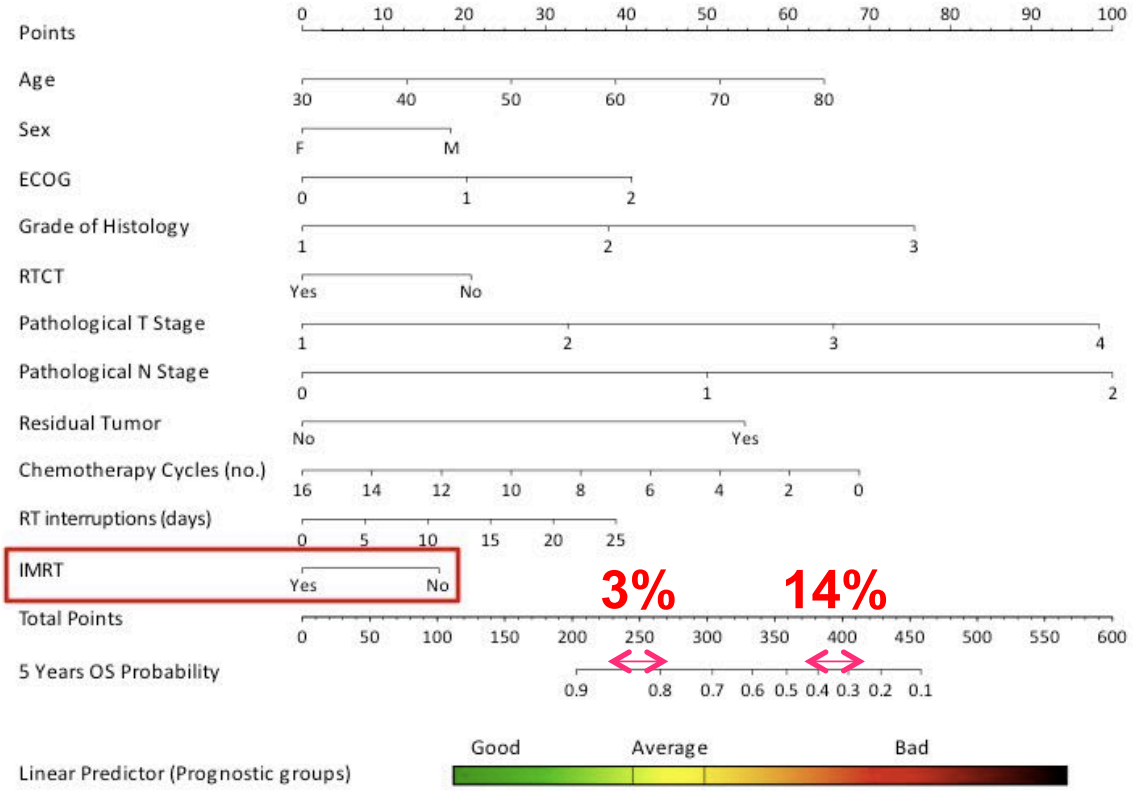
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli ART
Advanced Radiation Therapy

Postoperative RT in rectal cancer

Datamining Radiomics
KBO Labs
Knowledge Based Oncology Labs

- Cancer Institute Beijing 1798 pts



Gemelli ART
Advanced Radiation Therapy

Liu W et Al - *ASTRO* – 2014

Knowledge Based Oncology

Guidance for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

Gemelli ART
Advanced Radiation Therapy

CBER
Center for Biologics Evaluation and Research

Personalization by prediction models

Author	Journal	Institution	N° pts	Topic	Website
van Stiphout RG	Radiother Oncol, 2011	MAASTRO-UCSC Leuven-Rovigo	953	pCR	Y
Valentini V	JCO, 2011	UCSC- MAASTRO	2.795	LR, DM & **OS**	Y
Wang SJ	Ann Surg Oncol, 2011	Oregon University	42.830	**OS**	Y
Bowles TL	Dis Colon Rectum, 2013	MDAnderson	22.610	**OS**	Y
Russell MC	JAMA Surg, 2013	MDAnderson	85.190	R+	N
Peng J	PLoS One, 2014	Fudan University Shanghai	917	LR, DM & **OS**	N
van Stiphout RG	Radiother Oncol, 2014	MAASTRO-UCSC	190	pCR	N
Jwa E	Br J Cancer, 2014	Ulsan College of Medicine, Seoul	1.149	ypN	N
van Gijn W	Ann Oncol, 2015	Leiden University	2.281	DM & **OS**	N
Battersby N	Gut, 2015	Danish and UK	1.401	bowel dysfunction	N

Gemelli ART
Advanced Radiation Therapy

From Data Mining to Prediciton Model

- Clinical decision and covariates

- Prediction models in rectal cancer

- Transferability metric

Gemelli ART
Advanced Radiation Therapy

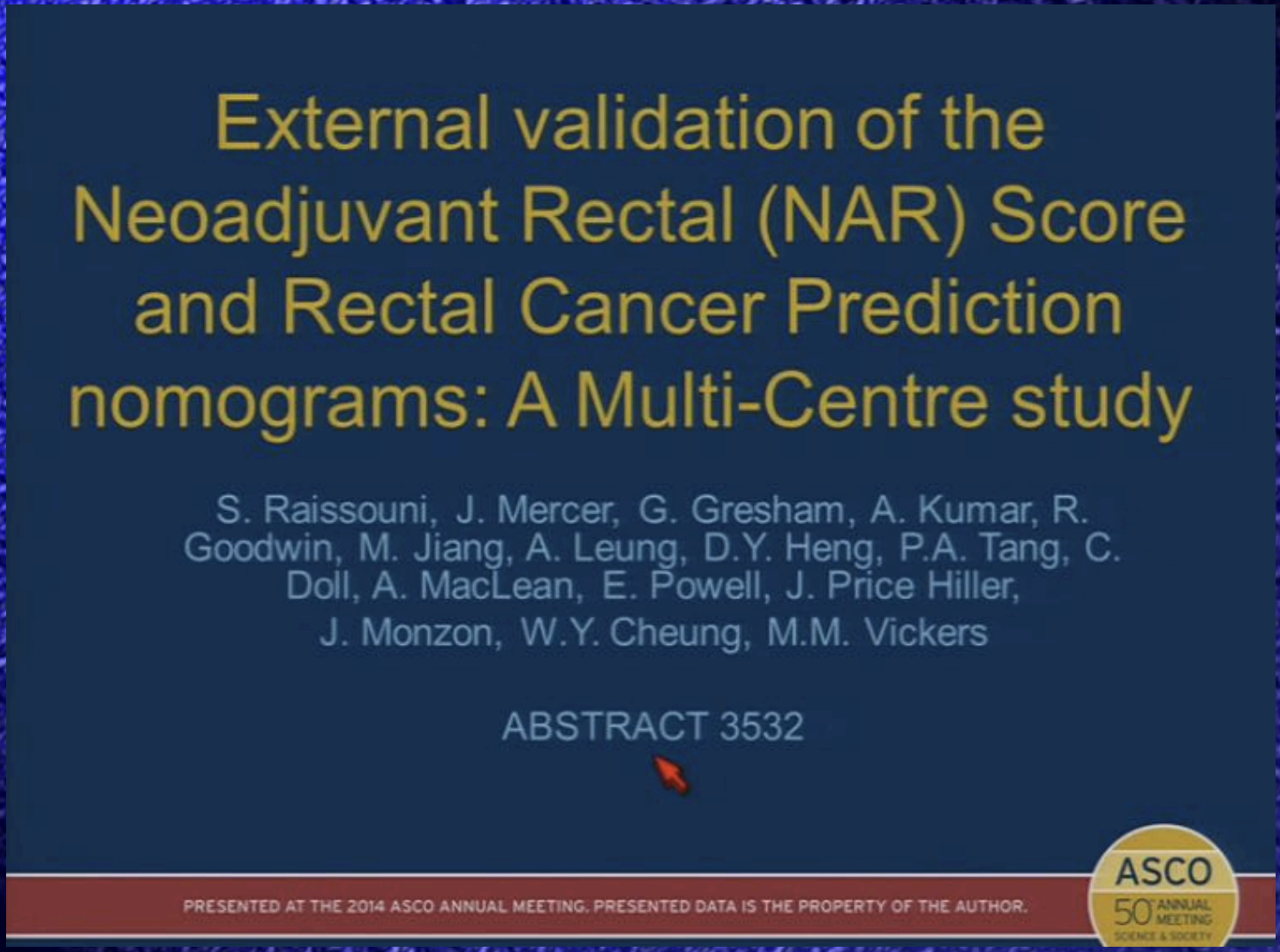
Accuracy and Generalizability

Measurement	Possible method	Measures?
Accuracy	Brier score	Predicted outcomes match observed?
Discrimination	Area under ROC	How well can we threshold predicted outcomes?
Calibration	Hosmer-Lemeshow	How do predicted values compare to subgroups of patients? (low/ medium/high probability)
Generalizability	DDM	Can we apply it to other datasets?
Reproducibility	DDM approx. 0.5	Similar population
Transferability	DDM < 0.5 >	Different population

Gemelli ART
Advanced Radiation Therapy

Van Soest J - MAASTRO

External validation



Gemelli ART
Advanced Radiation Therapy

Personalization by prediction models

Conclusions - Raissouni

- In a non-clinical trial population:
  - VPN predicted clinical outcomes (LR, DR, OS)
  - NAR was superior than pCR in predicting OS
    - May be a better endpoint than pCR in early phase clinical trials of LARC
  - VPN is better than NAR in discriminating clinical outcomes
    - Likely due to incorporation of other variables in VPN (type of surgery, chemotherapy, etc)

PRESENTED AT: ASCO 50 ANNUAL MEETING

Gemelli ART
Advanced Radiation Therapy

Personalization vs prediction models

Rectal Cancer

- Some of the Unknowns/Controversies
  - Who benefits from therapy beyond surgery alone
  - Who should get adjuvant chemotherapy after chemoRT and surgery

- None of these studies answer these questions
- Models may be more useful to be a surrogate in a trial to get answer faster
- We have more work to do to avoid treating patients who do not need it

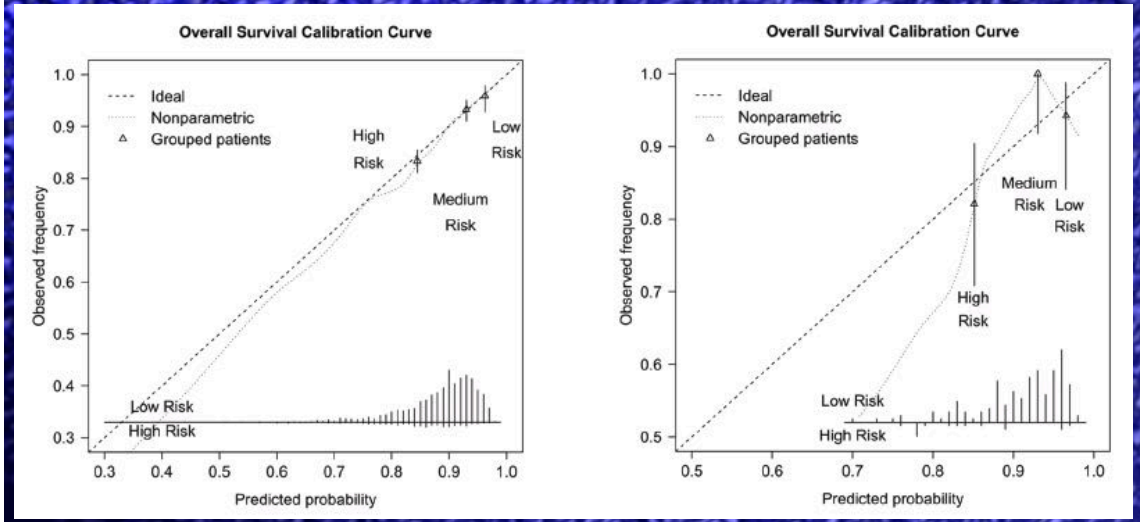
PRESENTED AT: ASCO 50

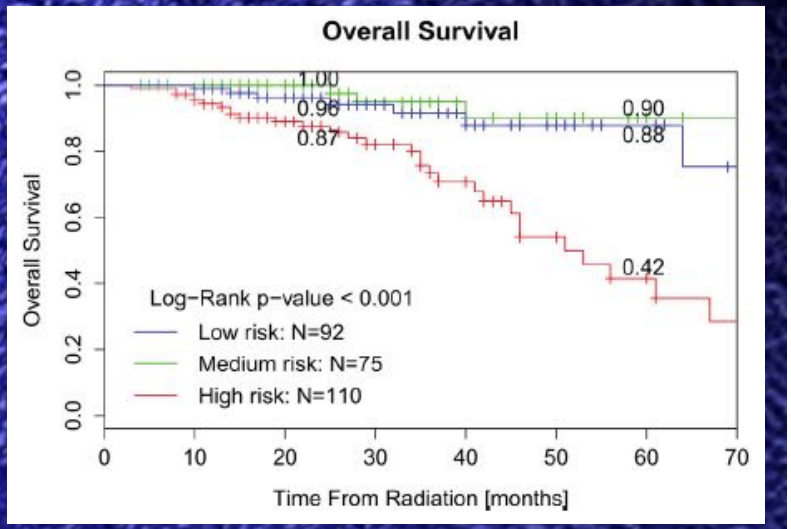
Gemelli ART
Advanced Radiation Therapy

External validation

Fudan University Shanghai Cancer Center, China

277 pts



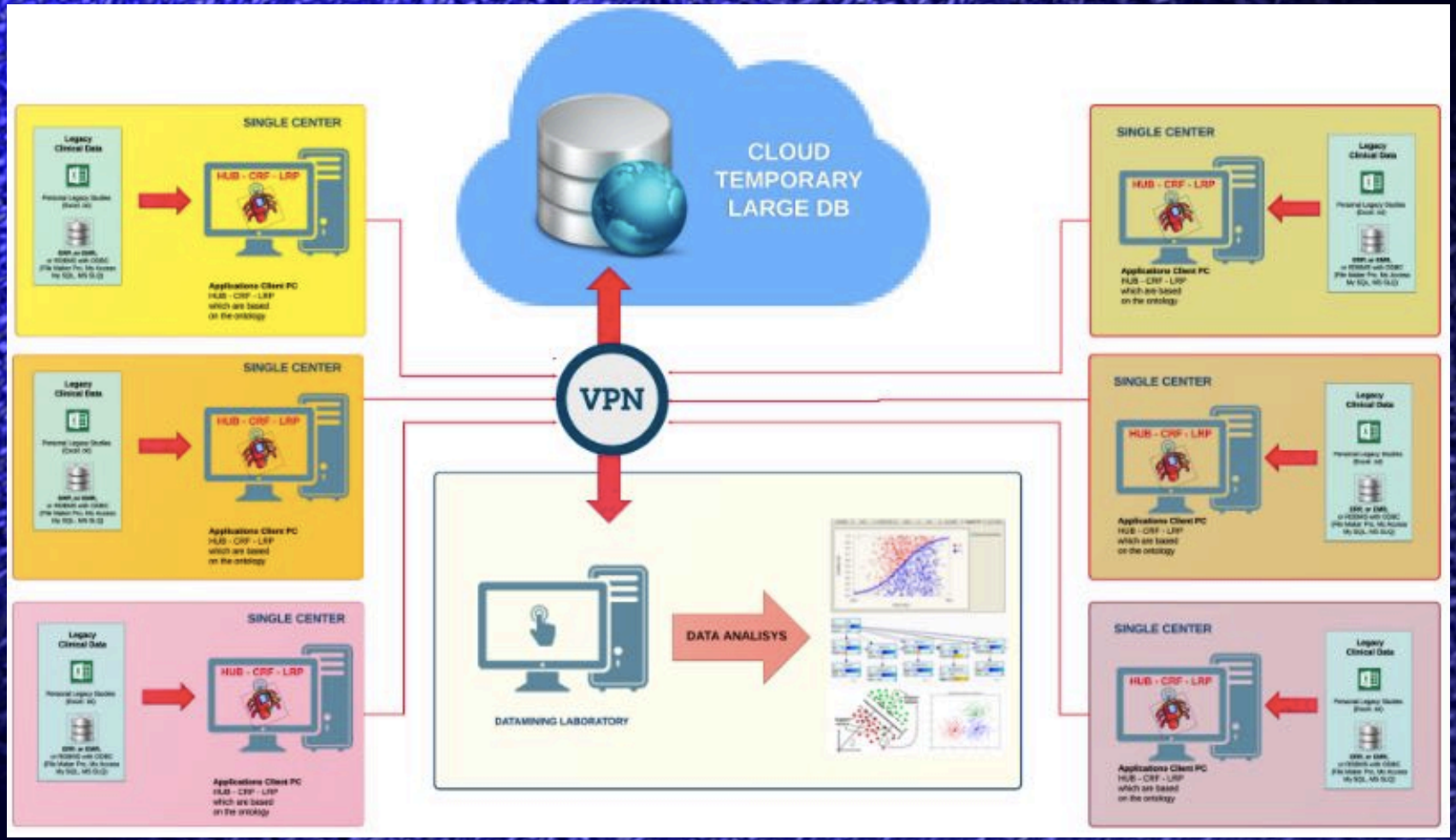


C-index = 0.72

Gemelli ART
Advanced Radiation Therapy

Shen L et Al – Oncotarget - 2015

EURECCA Italy: network for data mining



Gemelli ART
Advanced Radiation Therapy

Datamining
Radiomics
KBO Labs
Knowledge Based Oncology Labs

The issue of medicine

Medicine

is a science of uncertainty

and an art of probability

Gemelli ART
Advanced Radiation Therapy

Sir William Osler


ESTRO
35
29 April - 3 May 2016
Turin, Italy
WWW.ESTRO.ORG