Good responders: Who are they?

Apr 25th 2019

Hematology and Oncology

CHA Bundang Medical Center

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CHA HEALTH SYSTEMS

Introduction

Current practice after NAC in EBC

Patients who respond well to NAC (neoadjuvant chemotherapy) is often to proceed with the same breast and axillary procedures to patients who respond less

Is this idea realistic?

Selective elimination of breast cancer surgery in exceptional responders

History of organ sparing in oncology area

- ✓ Laryngeal ca
- ✓ Anal ca
- ✓ Cervix ca

AXLN mets with occult breast cancer

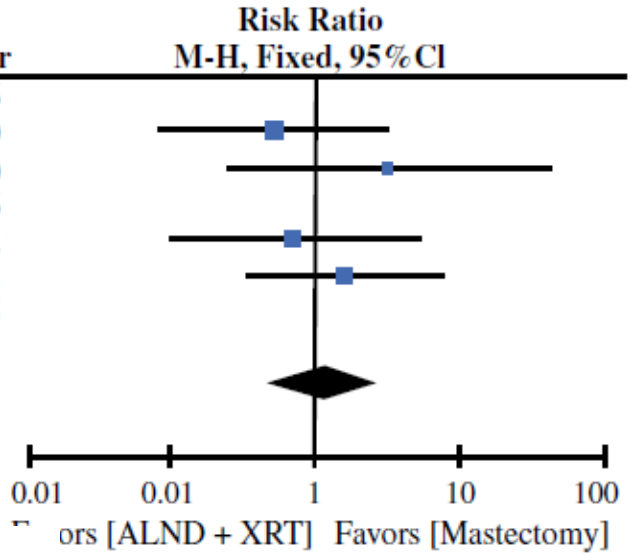
Locoregional recurrence

B

Study or Subgroup	ALND + XRT Events	Total	Mastectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Kemeny 1986	0	2	0	11		Not estimable	1986
Vlastos 2000	2	25	2	13	34.1%	0.52 [0.08, 3.28]	2000
Foroudi 2000	6	11	0	2	10.4%	3.25 [0.25, 43.03]	2000
Varadarajan 2006	0	8	0	1		Not estimable	2006
He 2012	1	13	7	64	30.7%	0.70 [0.09, 5.24]	2012
Woo 2013	3	11	2	12	24.8%	1.64 [0.33, 8.03]	2013
Rueth 2015	0	24	0	9		Not estimable	2015
Total (95% CI)		**94**		**112**	**100.0%**	**0.85 [0.42, 1.71]**	
Total events	12		11				

Heterogeneity $Chi^2 = 1.75$, $df = 3$ ($P = 0.63$); $I^2 = 0\%$

Test for overall effect: $Z = 0.27$ ($P = 0.78$)



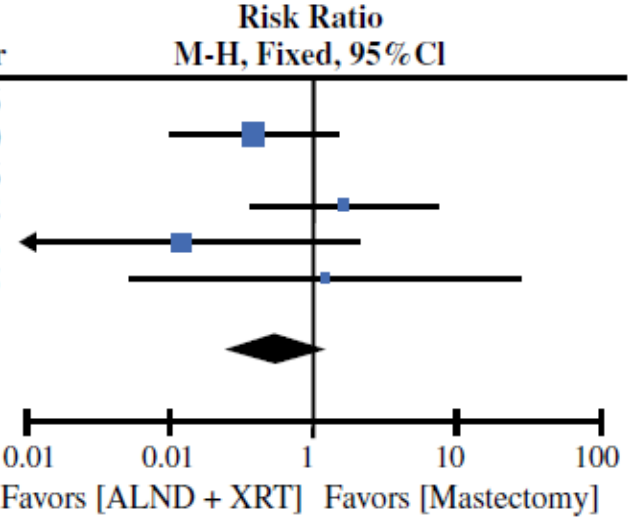
Distant recurrence

C

Study or Subgroup	ALND + XPT Events	Total	Mastectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Kemeny 1986	0	2	0	11		Not estimable	1986
Vlastos 2000	3	25	4	13	42.7%	0.39 [0.10, 1.49]	2000
Varadarajan 2006	0	8	0	1		Not estimable	2006
He 2012	2	13	6	64	16.4%	1.64 [0.37, 7.25]	2012
Woo 2013	0	11	4	12	35.1%	1.12 [0.01, 2.01]	2013
Rueth 2015	1	24	0	9	5.8%	1.20 [0.05, 27.05]	2015
Total (95% CI)		**83**		**110**	**100.0%**	**0.55 [0.24, 1.26]**	
Total events	6		14				

Heterogeneity $Chi^2 = 3.70$, $df = 3$ ($P = 0.30$); $I^2 = 19\%$

Test for overall effect: $Z = 1.41$ ($P = 0.16$)



(Macedo, Ann Surg Oncol 2016)

AXLN mets with occult breast cancer

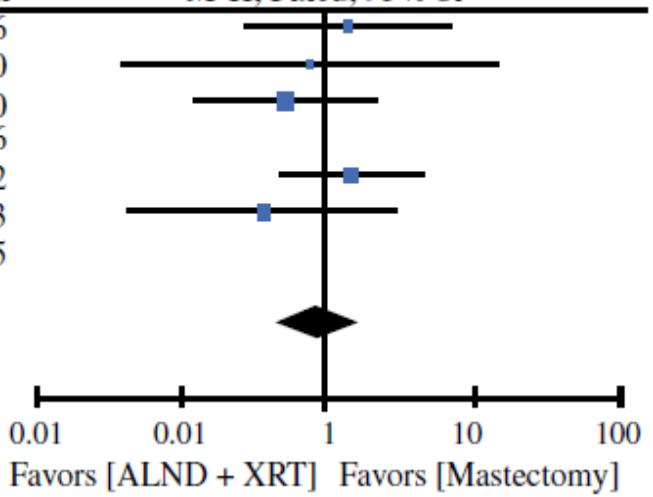
OS

A

Study or Subgroup	ALND + XPT Events	Total	Mastectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Kemeny 1986	1	2	4	11	10.1%	1.38 [0.28, 6.75]	1986
Foroudi 2000	1	11	0	2	6.5%	0.75 [0.04, 14.19]	2000
Vlastos 2000	3	25	3	13	32.3%	0.52 [0.12, 2.22]	2000
Varadarajan 2006	0	8	0	1		Not estimable	2006
He 2012	3	13	10	64	27.6%	1.48 [0.47, 4.64]	2012
Woo 2013	1	11	3	12	23.5%	0.36 [0.04, 3.00]	2013
Rueth 2015	0	24	0	9		Not estimable	2015
Total (95% CI)		**94**		**112**	**100.0%**	**0.85 [0.42, 1.71]**	
Total events	9		20				

Heterogeneity $Chi^2 = 2.32$, $df = 4$ ($P = 0.68$); $I^2 = 0\%$

Test for overall effect: $Z = 0.46$ ($P = 0.65$)



Absence of breast tumor on preop imagings saves mastectomy

(Macedo, Ann Surg Oncol 2016)

Terminology to describe test performance

Clinical response (Test)	Pathologic response (Outcome)	
	pCR	non-pCR
cCR	A	B
non-cCR	C	D

$$\text{Sensitivity} = \frac{A}{A+C}$$

$$\text{PPV} = \frac{A}{A+B}$$

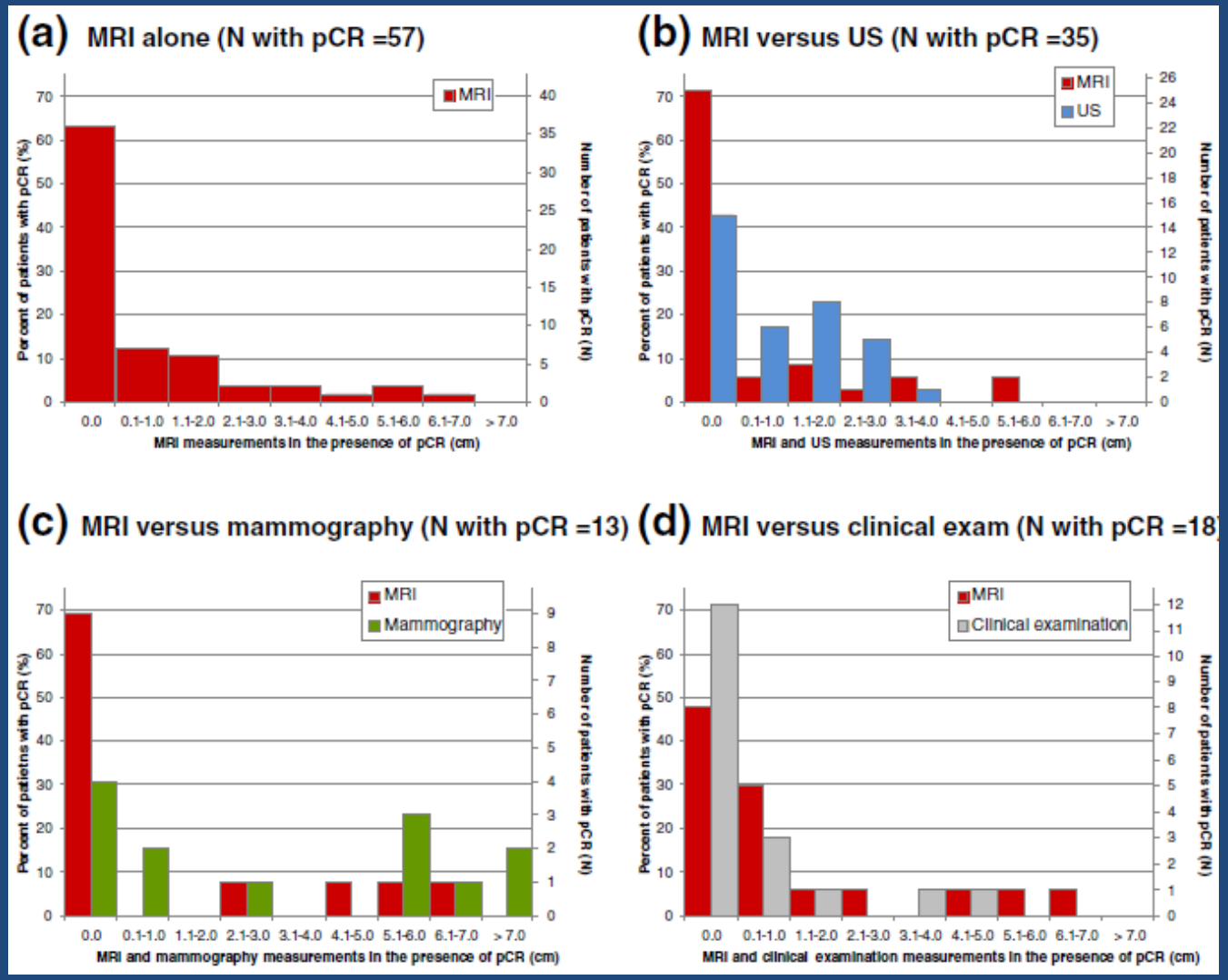
$$\text{Specificity} = \frac{D}{B+D}$$

$$\text{NPV} = \frac{C}{C+D}$$

MRI to predict pCR

MRI vs other methods to predict pCR

IPD meta-analysis (8 studies; N=300)



(Marinovich, BMC Cancer 2015)

ACRIN6657/I-SPY Trial: MRI to predict NAC response

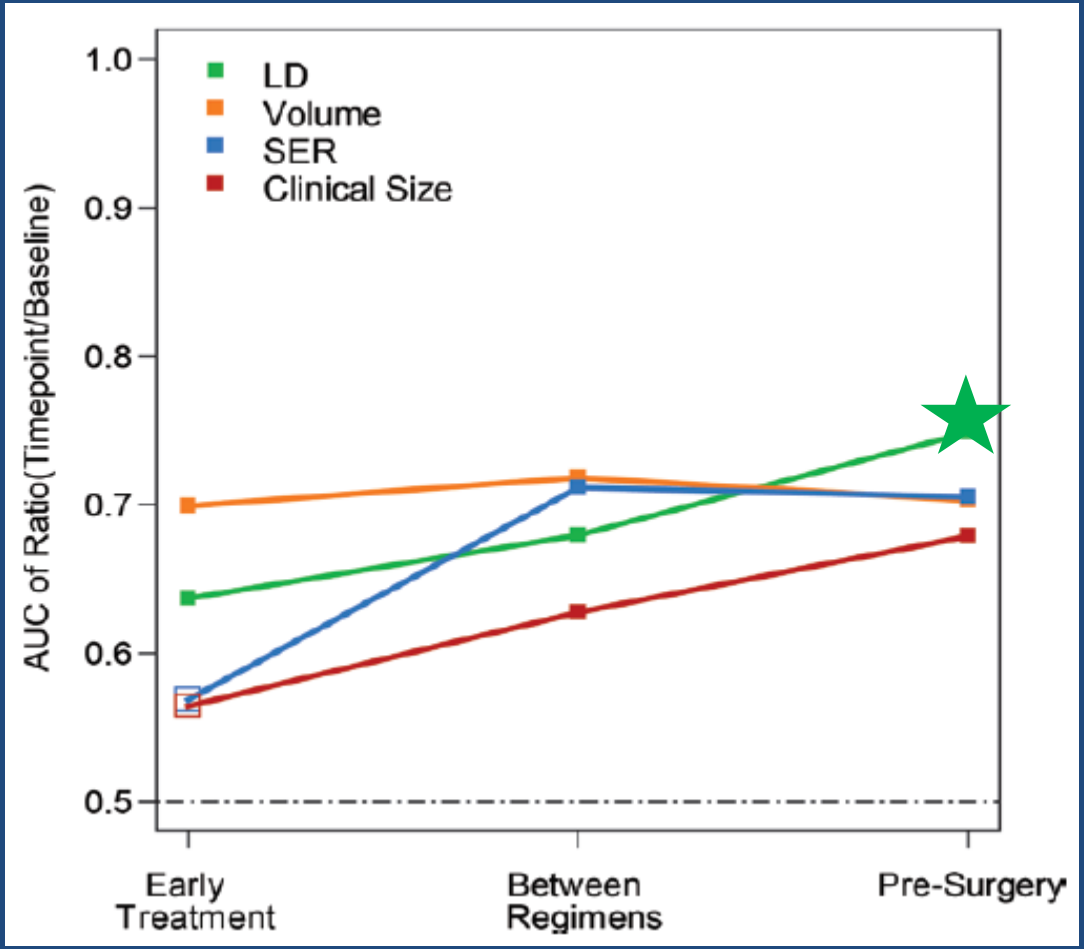
ACRIN: American College of Radiology Imaging Network

Stage II/III
May 2002~March 2006
N=216

(Hylton, Radiology 2012; 263: 663)

AUC for prediction of pCR

Ex) 0.7 indicates: TPR(sensitivity) is 0.7



Volume measurement shows higher predictability than LD measurement. However, it is just around 0.7

Insights Imaging (2013) 4:163–175
DOI 10.1007/s13244-013-0219-y

ORIGINAL ARTICLE

The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review

M. B. I. Lobbes · R. Prevos · M. Smidt · V. C. G. Tjan-Heijnen · M. van Goethem · R. Schipper · R. G. Beets-Tan · J. E. Wildberger

35 eligible studies

Sensitivity (%)	**25~100%**
Specificity (%)	50~97%
PPV (%)	47~73%
NPV (%)	71~100%

Correlation of tumor size on MRI and pathology

Author	Correlation coefficient	P-value
Partridge et al.	0.89	<0.001
Cheung et al.	0.982	<0.001
Martincich et al.	0.72	<0.001
Segara et al.	0.749	<0.0001
Kim et al.	0.645	<0.001
Moon et al.	0.584	NA
Wright et al.	0.49	NA
Park et al.	0.667	NA
Nakahara et al.	0.21	NS
Wang et al.	0.866	<0.01
Dongfeng et al.	0.698	<0.001
Fangberget et al.	0.87	<0.001
Guarneri et al.	0.53	NS
Shin et al.[a]	0.97	NA
Chen et al.	0.30	0.03
Kim et al.	0.619	<0.0001
Shin et al.[b]	0.781	NA

Median correlation coefficient 0.698

(Lobbes, Insights Imaging 2013)

Tri-modality imaging may augment accuracy for pCR prediction

cCR: Sum of score ≤ 5

NPV	0.87
PPV	0.95
Sensitivity	0.87
Specificity	0.93

Imaging Modality	Imaging Parameter Score			
	0	1	2	3
MR				
Early peak signal intensity		≤80	>80	
Internal enhancement pattern		Homogeneous	Heterogeneous	
Kinetic pattern		Type I	Type II	Type III
US				
Mass size	Resolution of mass	≤20 mm	>20 mm	
Mammography				
Residual mass	Absent	Present		
Malignant calcifications	Absent	Present		

(Umphrey, SABCS 2012, abs P3-03-03)

PET to predict pCR

Functional imaging

- Yeh showed palpation, mammo, US, and MRI had 19%, 26%, 35%, and 71% accuracy for prediction of pCR.
- Anatomic changes in tumor presentation are not reliable predictors of final pathologic state.
- Functional measurement of tumors (CE-MRI, MRS, PET) have shown substantial improvement over conventional anatomic imaging.

(Yeh, Am J Roentgenol 2015; 184:868; Tromberg, Cancer Res 2016)

FDG-PET results to predict pCR: a review (2013)

Author (ref)	*n*	Cycles/	Criteria	Sens (%)	Spec (%)	NPV (%)	PPV (%)
Bassa et al.[25]	15	1-2 cycles	Visual	75	100	NA	NA
Kim et al.[26]	50	4 cycles	79% ΔSUV_{max}	85	83	83	85
Smith et al.[27]	30	1 cycle	20% ΔSUV_{max}	90	74	94	64
Schelling et al.[28]	22	1 cycle	55% ΔSUV_{max}	100	85	NA	NA
		2 cycles	55%ΔSUV_{max}	83	94	NA	NA
Rousseau et al.[31]	64	2 cycles	60% ΔSUV_{max}	89	96	87	97
Berriolo-Riedinger et al.[32]	47	1 cycle	60% $\Delta SUV_{max\text{-}BSA\text{-}G}$	75	92	94	75
McDermott et al.[33]	96	1cycle	24%ΔSUV_{max}	100	53	NA	NA
		Mid-NCT	58%ΔSUV_{max}	100	68	NA	NA
		End-NCT	64%ΔSUV_{max}	100	71	NA	NA
Kumar et al.[35]	23	2 cycles	50%ΔSUV_{max}	93	75	86	87.5
Schwarz-Dose et al.[36]	69	1 cycle	45%ΔSUV_{max}	73	63	90	36
Schneider-Kolsky et al.[37]	60	4 cycles	75%ΔSUV_{max}	78	60	90	37
Jung et al.[38]	66	4 cycles	35.5%ΔSUV_{peak}	96.5	89	NA	NA
Keam et al.[39]	78	1 cycle	50%ΔSUV_{max}	85.7	61	95	32.4
Kolesnikov-Gauthier et al.[40]	63	1 cycle	15%ΔSUV_{max}	53	84	62	79
Groheux et al.[41]	20	2 cycles	42% ΔSUV_{max}	64	100	83	100
Humbert et al.[42]	125	1 cycle	75% ΔSUV_{max}	64	83	79	69
Duch et al.[43]	50	4 cycles	52%ΔSUV_{max}	86	90	NA	NA

(Kostakoglu, Semin Nuc Med 2013)

The Oncologist®

Breast Cancer

(Sheikhbahaei, Oncologist **2016**: 21:931)

FDG-PET/CT and MRI for Evaluation of Pathologic Response to Neoadjuvant Chemotherapy in Patients With Breast Cancer: A Meta-Analysis of Diagnostic Accuracy Studies

Sara Sheikhbahaei,[a] Tyler J. Trahan,[a] Jennifer Xiao,[a] Mehdi Taghipour,[a] Esther Mena,[a] Roisin M. Connolly,[b] Rathan M. Subramaniam[a,c,d,e,f]

Author, year	Index test	Use of Contrast	Scanner (manufacturer)	Time of scan	Patients, no.[a]	Image interpretation	Blind	Response assessment parameter (threshold %, analysis)	pCR, no.
An e 6]	PET/CT	NR	Biograph Duo or Biograph Truepoint (Siemens)	Baseline–post-NAC	16	1 radiologist	No	ΔSUV (80.6%, ROC)	3
	DCE-MRI DWI-MRI	Yes	3.0 T Magnetom Verio (Siemens)	Baseline–post-NAC	20	1 radiologist	NR	ΔLD (87.7%, ROC)	3
Pah 201	PET/CT	NR	Gemini TF (Philips)	Baseline–interim NAC (3 or 4 cycles)	21	2 experienced nuclear physicians	NR	ΔSUV (69%, ROC)	7
	MRI	Yes	3.0-T Achieva (Philips)	Baseline–interim NAC (3 or 4 cycles)	21	1 experienced radiologist	NR	ΔLD (38.2%, ROC)	7
Pengel et al., 2014 [18]	FDG-PET/CT	NR	Gemini TF (Philips)	Baseline–interim NAC (3 cycles)	93	Experienced panel	NR	ΔSUV (80%, ROC)	43
	MRI	Yes	3.0-T Achieva (Philips)	Baseline–interim NAC (3 cycles)	93	1 experienced radiologist	NR	ΔLD (75%, ROC)	43
Kim 201	PET/CT	No	Discovery ST scanner (GE Healthcare)	Baseline–post-NAC	38	2 nuclear medicine physicians	Yes	ΔSUV (60.1%, ROC)	23
	MRI	Yes	1.5-T Signa (GE Healthcare) or 3-T Achieva (Philips)	Baseline–post-NAC	56	2 radiologists	Yes	ΔLD (50%, ROC)	34
Simo et al., 2013 [20]	FDG-PET	NR	NR	Baseline–post-NAC	30	NR	NR	EORTC (NR)	16
	MRI	NR	NR	Baseline–post-NAC	24	NR	NR	RECIST 1.1 (NR)	12
Tateishi et al., 2012 [13]	PET/CT	NR	Biograph 16 (Siemens) or Aquiduo PCA-7000B (Toshiba)	Baseline–interim NAC (2 cycles)	142	2 nuclear medicine physicians	NR	EORTC (CR vs. PR, SD, PD)	24
	DCE-MRI	Yes	Magnetom Trio, A Tim System (Siemens)	Baseline–interim NAC (2 cycles)	142	1 MR technologist, 1 radiologist	NR	RECIST (CR vs. PR, SD, PD)	24
Par 201	PET/CT	No	Gemini (Philips)	Baseline–post-NAC	34	2 nuclear medicine physicians	Yes	ΔSUV (63.9%, ROC)	7
	DWI-MRI	Yes	1.5 T Signa (GE Medical Systems)	Baseline–post-NAC	34	2 radiologists	Yes	ADC (54.9%, ROC)	7
Cho 201	PET/CT	NR	NR	Baseline–post-NAC	41	2 physicians	Yes	ΔSUVpeak (50%)	7
	MRI	No	NR	Baseline–post-NAC	29	NR	NR	RECIST (CR vs. PR, SD)	7
Dose-Schwarz et al., 2010 [15]	PET	No	ECAT951R/31 ECATExact47 ECATExactHR + (Siemens)	Post-NAC	89	Blind	Yes	SUV (1.5, NR)	16
	MRI	Yes	NR	Baseline–post-NAC	46	Experienced radiologists	NR	Visual interpretation	5
Mukherjee et al., 2010 [21]	PET	No	NR	Baseline–post-NAC	31	NR	NR	Visual interpretation (5-point scale)	5
	MRI	Yes	NR	Baseline–post-NAC	27	NR	NR	ΔLD (50%, NR)	5

MRI vs FDG-PET to predict pCR

Parameter	Studies, no. (patients, no.)	Sensitivity (95% CI), I^2, %	Specificity (95% CI), I^2, %
All studies			
MRI	10 (492)	0.88 (0.76–0.95), 78	0.55 (0.41–0.68), 49
FDG-PET or FDG-PET/CT	10 (535)	0.71 (0.52–0.85), 87	0.77 (0.58–0.89), 73
FDG-PET/CT	7 (385)	0.82 (0.62–0.92), 86	0.79 (0.52–0.93), 79
FDG-PET alone	3 (150)	0.43 (0.26–0.63), 67	0.73 (0.44–0.91), 48
Intra-NAC assessment			
MRI	3 (256)	0.89 (0.66–0.97), 83	0.42 (0.20–0.68), 69
FDG-PET/CT	3 (256)	0.91 (0.86–0.95), 0	0.69 (0.25–0.93), 87
Post-NAC assessment			
MRI	7 (236)	0.88 (0.71–0.96), 75	0.63 (0.51–0.74), 0
FDG-PET or FDG-PET/CT	7 (279)	0.57 (0.40–0.71), 73	0.80 (0.65–0.90), 29
FDG-PET/CT	4 (129)	0.71 (0.42–0.89), 79	0.88 (0.73–0.95), 0

In the intra-NAC setting, PET outperformed MRI in terms of specificity.
In the post-NAC setting, MRI showed higher diagnostic accuracy than PET in terms of sensitivity.

Experimental methods to predict pCR

BJC

British Journal of Cancer (2015) 113, 1565–1570 | doi: 10.1038/bjc.2015.381

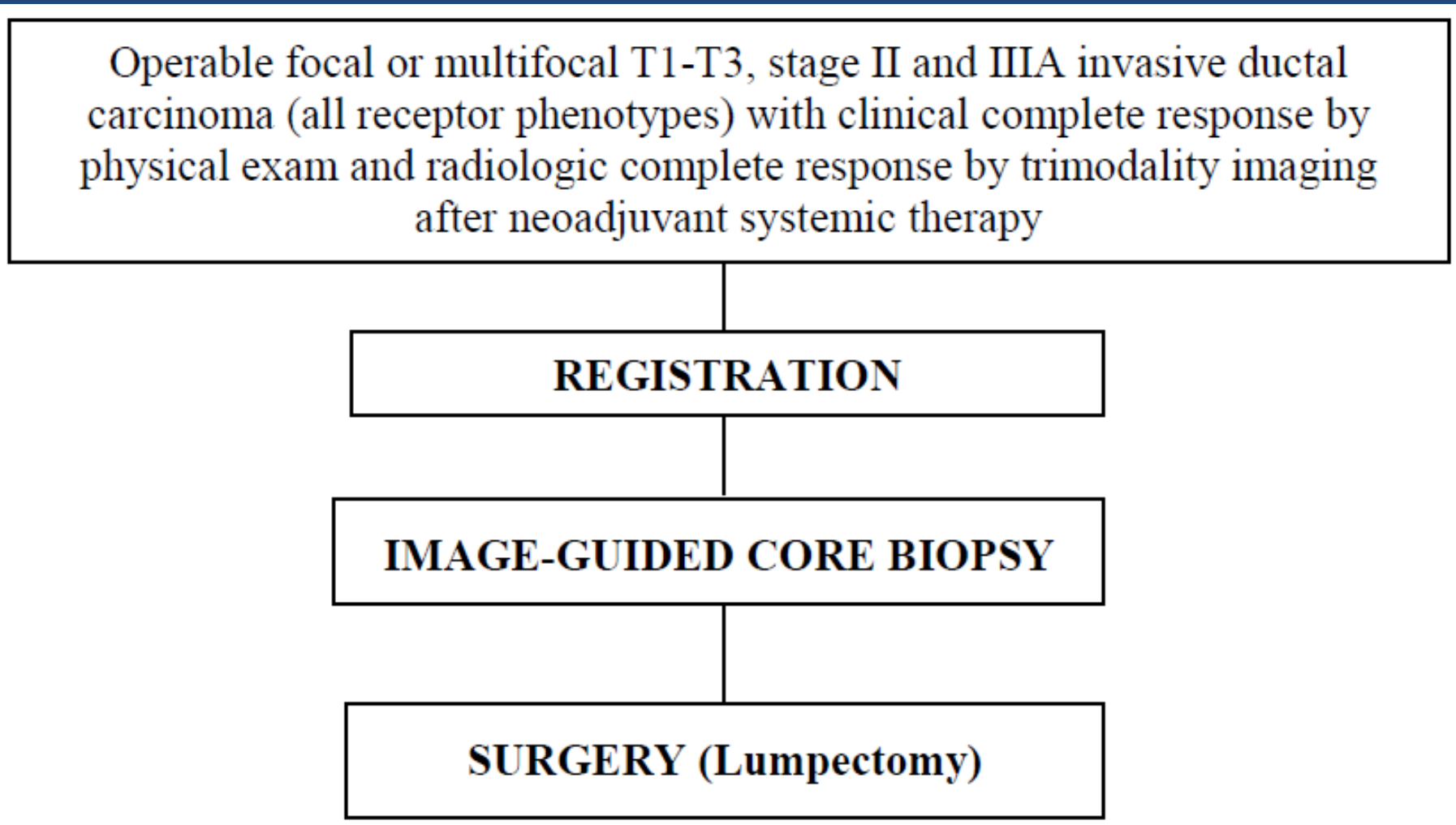
Keywords: Invasive breast cancer; neoadjuvant chemotherapy; pathological complete response; minimal invasive biopsy

Diagnosis of pathological complete response to neoadjuvant chemotherapy in breast cancer by minimal invasive biopsy techniques

Prospective study

	All (n=116)	Mammo-guide Bx (n=16)
NPV	71.3%	100%
FNR	49.3%	0%

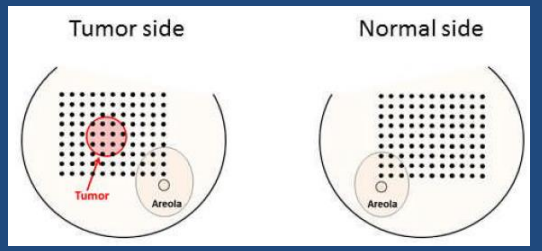
Phase II trial of image-guided biopsy: NRG-BR005

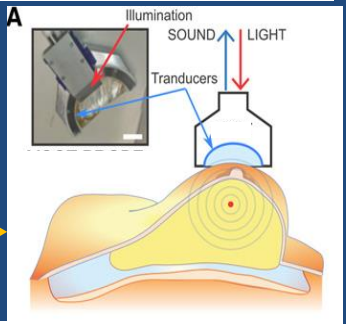


Ongoing

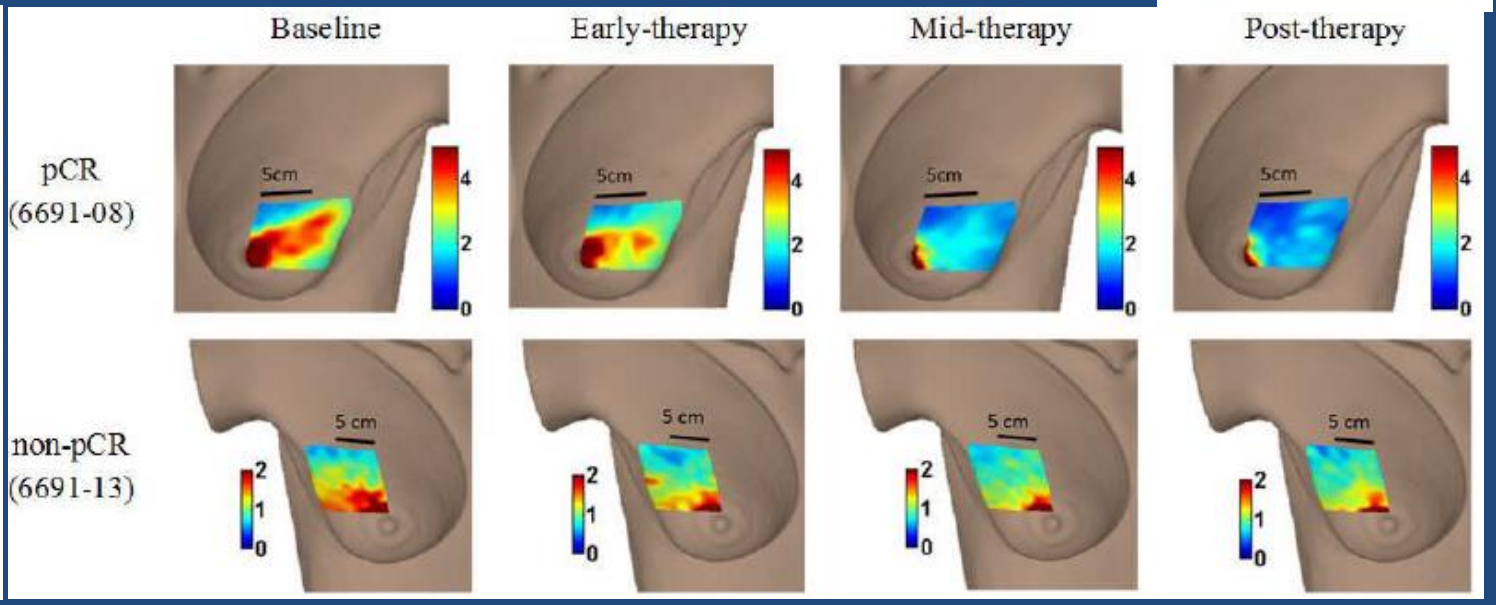
DOSI: Diffuse Optical Spectroscopic Imaging

-High resolution spectroscopy from 650nm-1000nm
-OxyHb, deoxyHb, water, and lipid have prominent absorption features
-May differentiate cancer and normal tissues
-TOI (Tissue Oxygenation Index)=deoxy-Hb X H2O/lipid





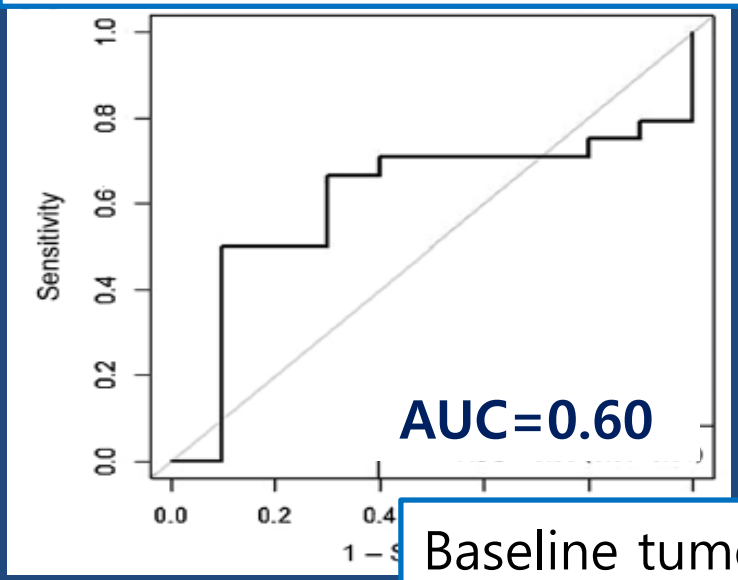
Non-invasive bed-side imaging →



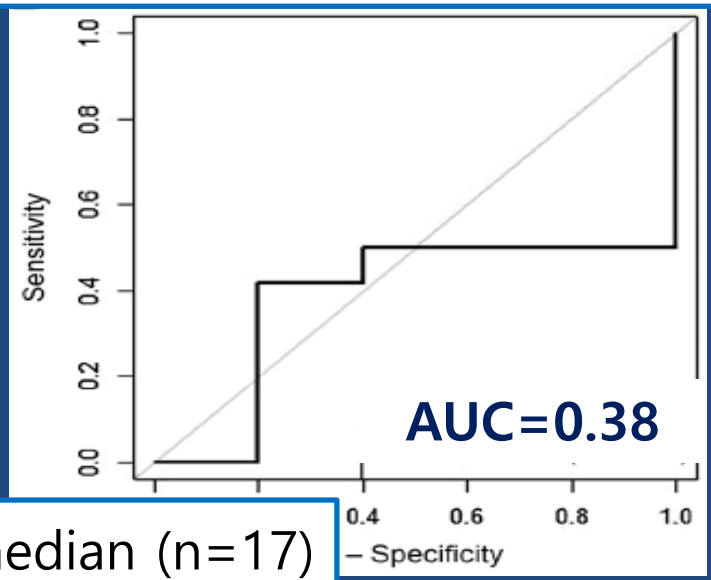
(Tromberg, Cancer Res 2016)

ROC curves for pCR using $\%TOI_{TN}$

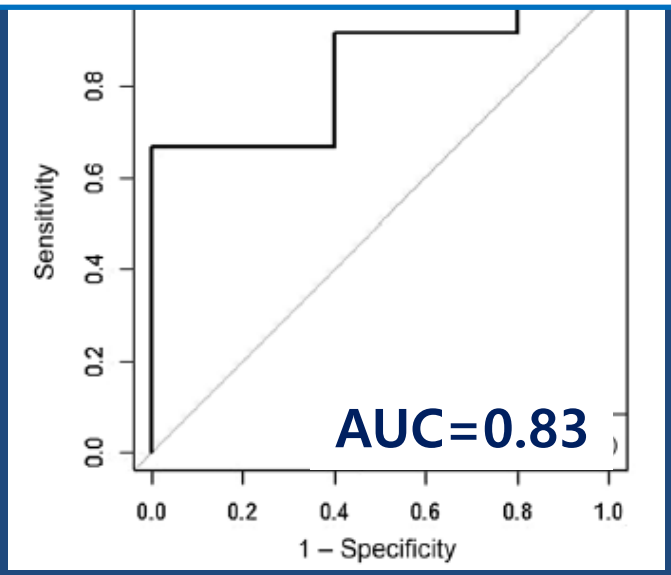
All pts (n=34)



Baseline tumor sat ≤median (n=17)



Baseline tumor sat >median (n=17)



(Tromberg, Cancer Res 2016)

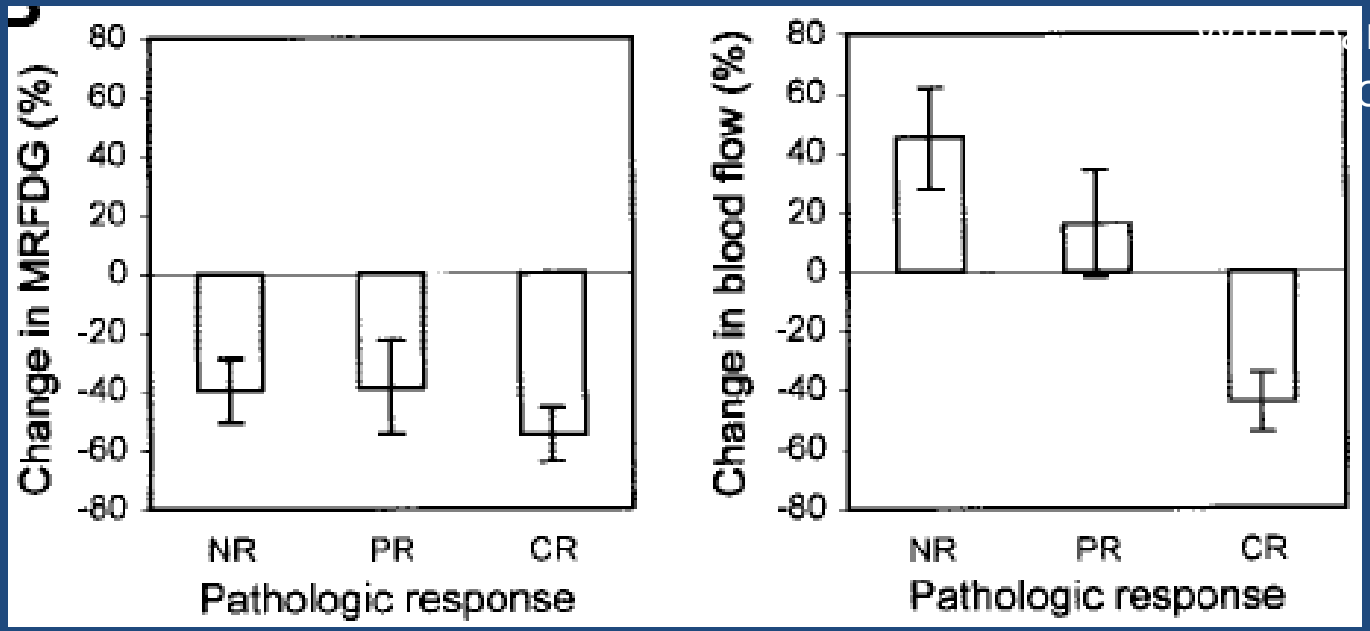
Changes in Blood Flow and Metabolism in Locally Advanced Breast Cancer Treated with Neoadjuvant Chemotherapy

David A. Mankoff, MD, PhD[1]; Lisa K. Dunnwald, BS[1]; Julie R. Gralow, MD[2]; Georgiana K. Ellis, MD[2]; Erin K. Schubert, BA[1]; Jeffrey Tseng, MD[1]; Thomas J. Lawton, MD[3]; Hannah M. Linden, MD[2]; and Robert B. Livingston, MD[2]

MRFDG and blood flow by pathologic response

N=34

Metabolism imaging: ^{18}F-FDG
Blood flow imaging: tracer (^{15}O-H2O) was administered



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on

(J Nucl Med 2003; 44: 1806)

OXFORD

JNCI J Natl Cancer Inst (2018) 110(6): djy018

doi: 10.1093/jnci/djy018
First published online April 12, 2018
Meta-Analysis

Circulating Tumor Cells in Breast Cancer Patients Treated by Neoadjuvant Chemotherapy: A Meta-analysis

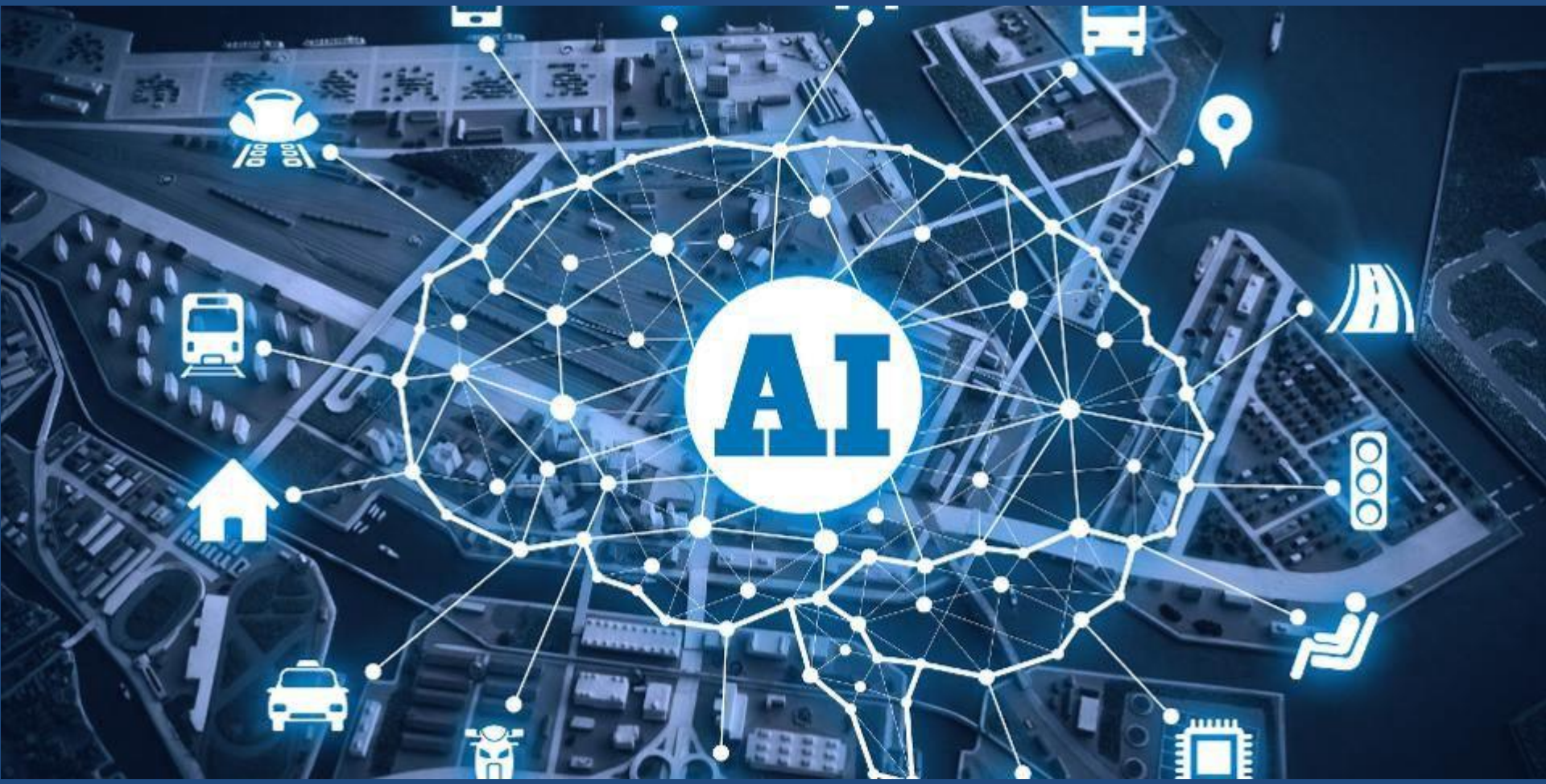
CTC(≥1) before surgery does not predict pCR

	N patients (%)	0 CTC N (%)	≥1 CTC N (%)	p value
CTC count before neoadjuvant chemotherapy				
pCR	1557 (100)			**p=0.08**
No			311 (26.3)	
Yes			81 (21.7)	
pCR (T4d excluded)	1359 (100)			**p=0.01**
No	1060 (78.0)	803 (75.8)	257 (24.2)	
Yes	299 (22.0)	247 (82.6)	52 (17.4)	
CTC count before surgery				
pCR	1141 (100)			**p=0.45**
No			132 (15.7)	
Yes			41 (13.7)	
pCR (T4d excluded)	954 (100)			**p=0.83**
No	723 (75.8)	616 (85.2)	107 (14.8)	
Yes	231 (24.2)	199 (86.1)	32 (13.9)	

CTC before NAC

CTC before surgery

	Before NAC	Before surgery
Sensitivity	82.6%	86.1%
Specificity	24.2%	14.8%
PPV	23.5%	24.4%
NPV	83.2%	76.9%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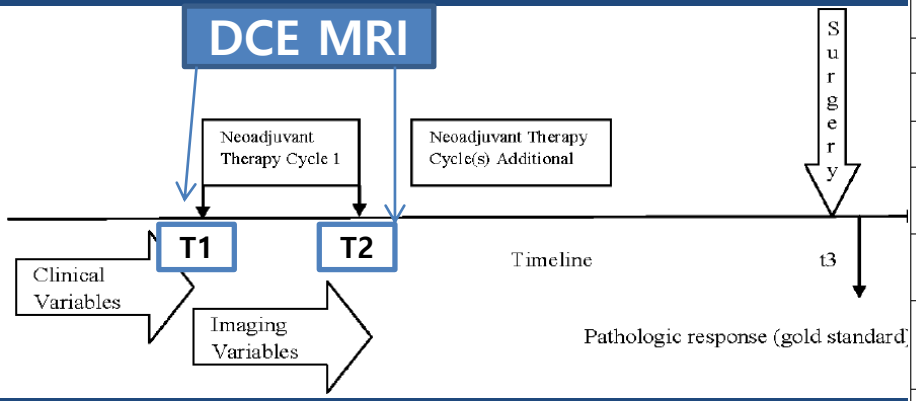
AMIA Annu Symp Proc. 2011; 2011: 868–877.
Published online 2011 Oct 22.
PMCID: PMC3243164
PMID: 22195145

Early Prediction of the Response of Breast Tumors to Neoadjuvant Chemotherapy using Quantitative MRI and Machine Learning

Subramani Mani, MBBS, PhD, Yukun Chen, MS, Lori R. Arlinghaus, PhD, Xia Li, PhD, A. Bapsi Chakravarthy, MD, Sandeep R. Bhave, BS, E. Brian Welch, PhD, Mia A. Levy, MD, PhD, and Thomas E. Yankeelov, PhD

Temporal relationship of clinical and imaging parameters



List of clinical and imaging variables

Clinical variable	Description	Imaging variable	Key Term	Description
Age	Age at the time of diagnosis	Delta ADC	Delta	t1, t2 difference
ER+	Estrogen receptor	Delta K^{trans} FXL	K^{trans}	Pharmacokinetic transfer constant
PR+	Progesterone receptor	Delta K^{trans} FXLvp	FXL	Fast exchange limit
HER2+	Human epidermal growth factor receptor	Delta K^{trans} FXR	FXR	Fast exchange regime
Clinical Grade	Pretreatment clinical grade	Delta v_e FXL	v_p	Blood plasma volume fraction
Proliferative rate		Delta v_e FXLvp	v_e	Extravascular extracellular volume fraction
Pre-treatment nodal status	Pathologically confirmed by fine needle aspiration or sentinel node evaluation	Delta v_e FXR	t_i	Intra cellular water lifetime of water molecule
Clinical-T	Pretreatment clinical size based on clinical findings judged most accurate for that case (physical exam, ultrasound, mammogram, conventional MRI)	Delta v_p FXL		
Clinical-N	Pretreatment nodal stage based on pathologically confirmed by fine needle aspiration of node or sentinel evaluation	Delta t_i FXR		
Pre-treatment clinical stage	Staging of the breast cancer prior to initiation of systemic chemotherapy	K^{trans} t_i FXL		
Pre-treatment physical exam	Longest diameter by physical exam (cm)	K^{trans} t_i FXLvp		
Pre-treatment longest diameter (ultra sound)	Longest dimension (cm) Clinical judgment is used to determine the modality most accurate for that case (physical exam, ultrasound, mammogram, conventional MRI)	K^{trans} t_i FXR		
		Delta tumor volume		

Machine learning finds the best predictive model

Imaging + Clinical Data (25 variables)	Accuracy		Precision		Recall/Sensitivity		Specificity		AUC	
Algorithm	No-FS	GS-10	No-FS	GS-10	No-FS	GS-10	No-FS	GS-10	No-FS	GS-10
Naïve Bayes	0.55	0.55	**1.00**	0.60	0.18	0.55	**1.00**	0.56	0.70	0.69
CART	0.45	0.70	0.50	0.73	0.55	0.73	0.33	0.67	0.42	0.68
SVM	0.70	0.65	0.78	0.67	0.64	0.73	0.78	0.56	0.78	0.78
RF	0.70	0.65	0.78	0.70	0.64	0.64	0.78	0.67	0.79	0.71
LR	0.70	0.75	0.78	0.80	0.64	0.73	0.78	0.78	0.69	0.81
Bayesian LR	**0.90**	0.75	0.91	0.80	**0.91**	0.73	0.89	0.78	**0.96**	0.82

Why is prediction of pCR so hard?

Factors affecting on MRI accuracy

✓ Subtype may affect the predictability
-Luminal type: hard to predict pCR d/t low pCR rate

✓ Regimens may affect
-Antivascular effects of taxane may underestimate residual tumor size d/t less enhancement on contrast-enhanced MRI

✓ Presence of DCIS

✓ Responding process may be heterogeneous

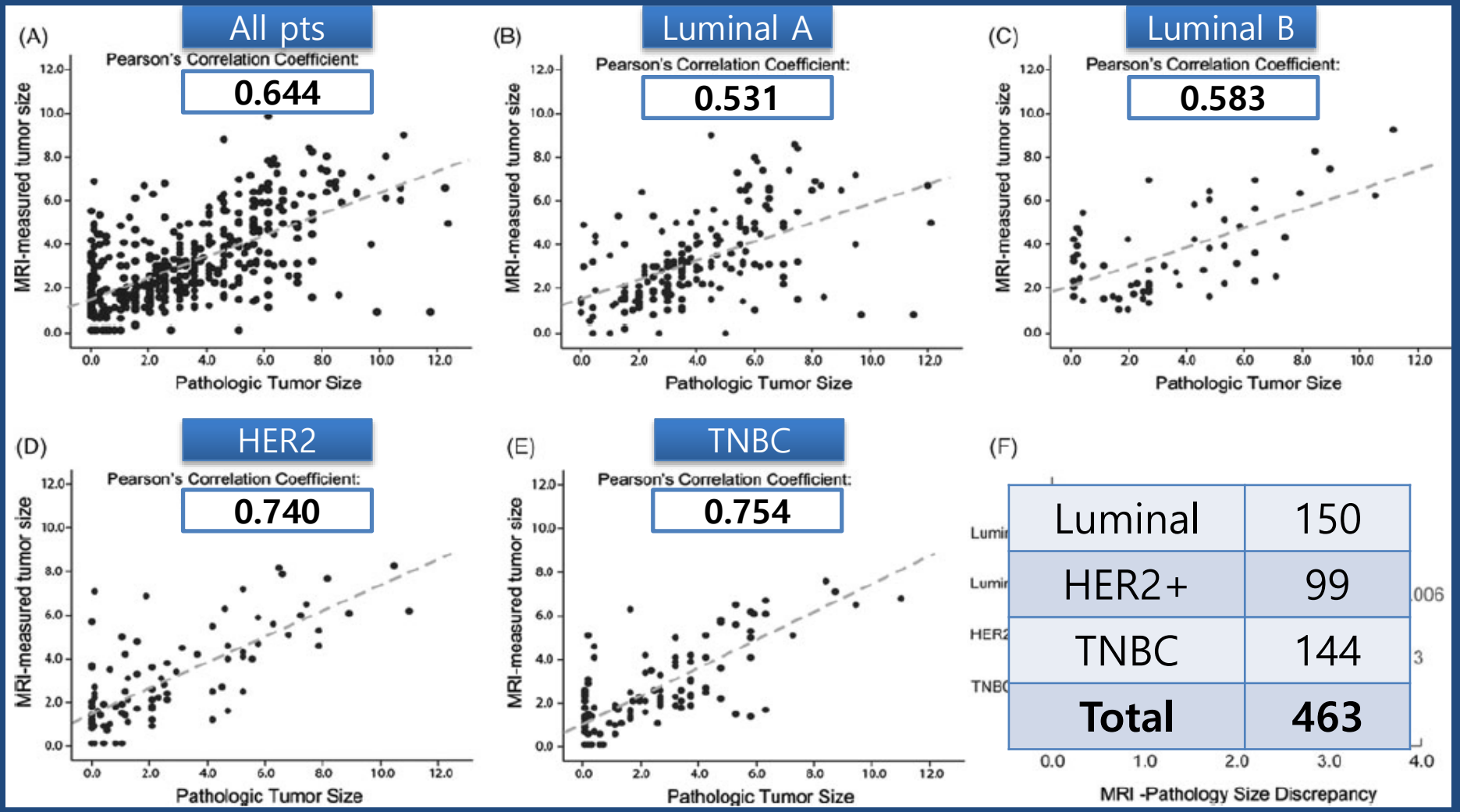
(Denis, EJSO 2004; 30 :1069)

Take Home Messages

- If we have accurate methods to predict pCR before surgery, we might omit breast surgery
- However, currently we don't have a golden method
- DCE-MRI is one of better imagings so far in this regard
- I expect that preoperative pCR-predicting method will be developed by incorporating new functional/metabolic imagings and AI technology

Subtype affects accuracy of prediction of pCR

Accuracy of MRI in predicting residual tumor extent
→ high in TNBC/HER2+, low in HR+



(Moon, Ann Surg 2013; 257: 133)