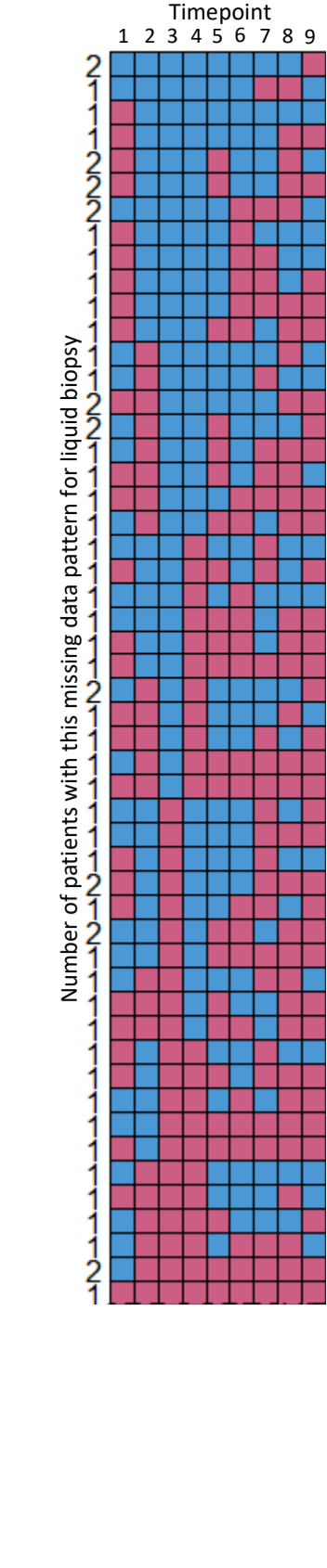


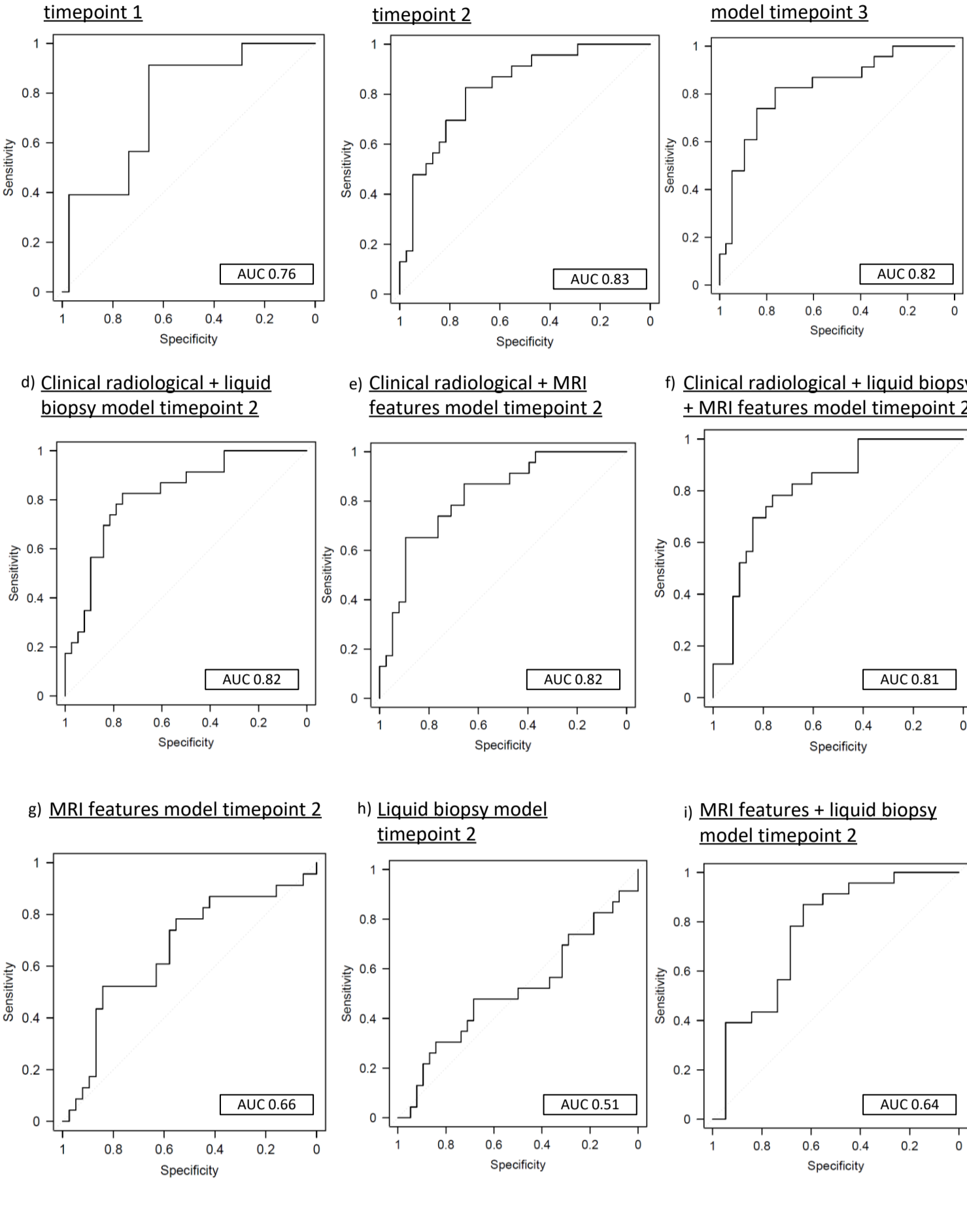
Supplementary figure 1

Plot on missing liquid biopsy samples. Each horizontal row represent a missing data pattern and how many times it occurred. Each vertical row represents a timepoint at which a liquid biopsy was collected. A blue square means the sample was available for analysis, a red square means it was missing.



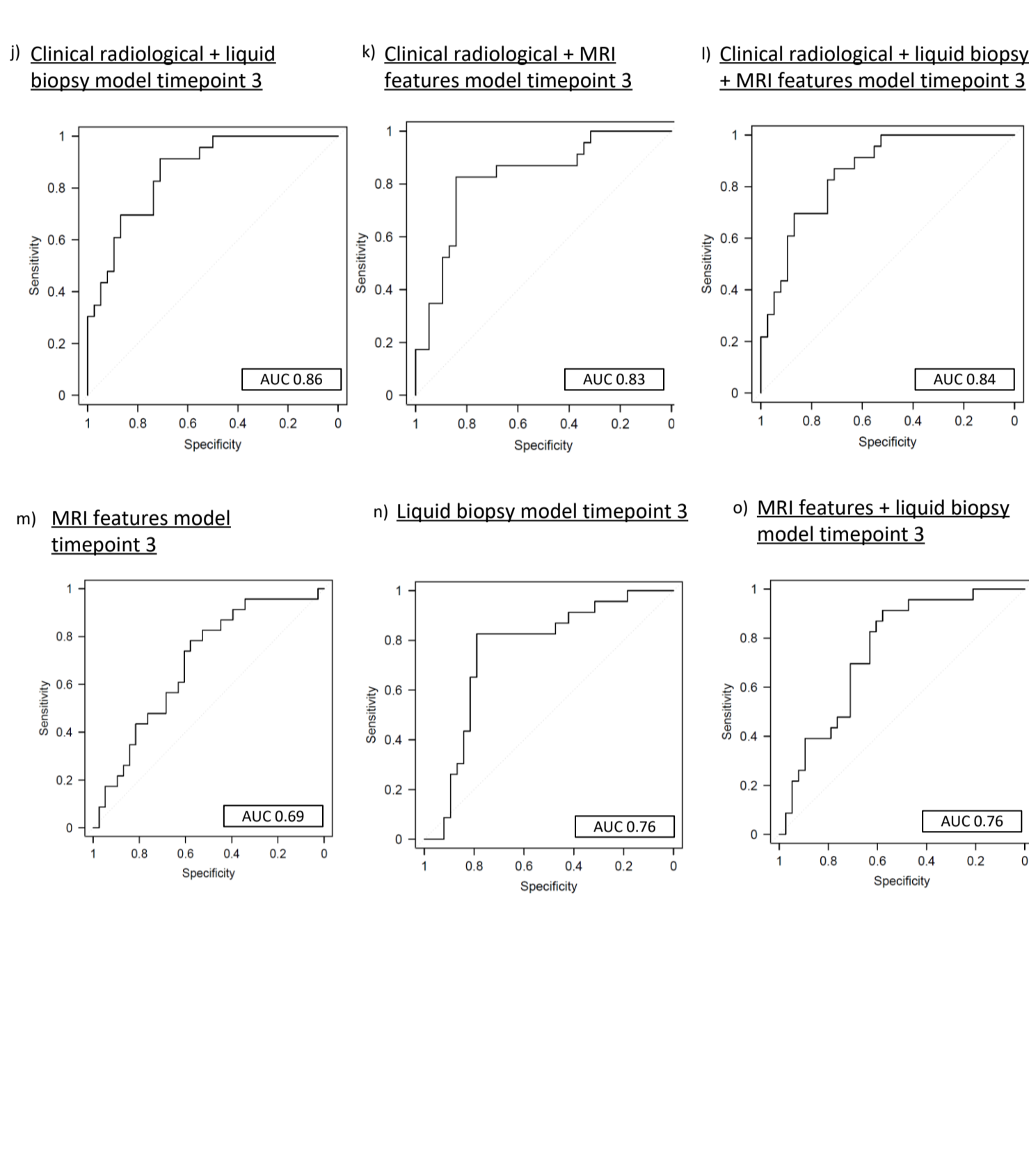
Supplementary figure 2

ROC curves of models at timepoint 1 (a), timepoint 2 (b, d-i) and timepoint 3 (c, j-o) discriminating between pCR (RCB=0) and residual disease (RCB>0). Sensitivity = the % of patients with pCR correctly classified by the model. Specificity = the % of patients with residual disease correctly classified by the model



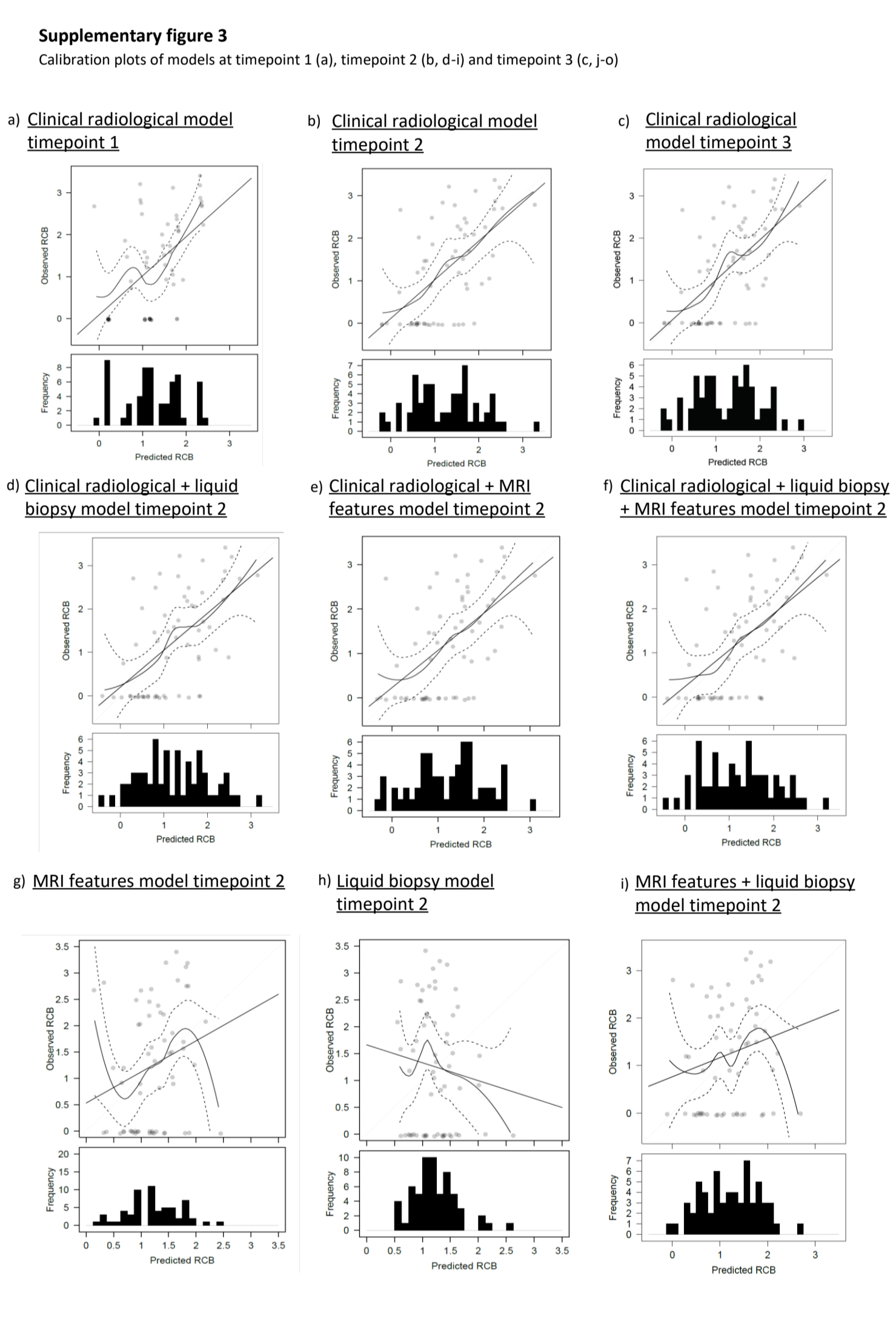
Supplementary figure 2 (continued)

ROC curves of models at timepoint 1 (a), timepoint 2 (b, d-i) and timepoint 3 (c, j-o) discriminating between pCR (RCB=0) and residual disease (RCB>0). Sensitivity = the % of patients with pCR correctly classified by the model. Specificity = the % of patients with residual disease correctly classified by the model



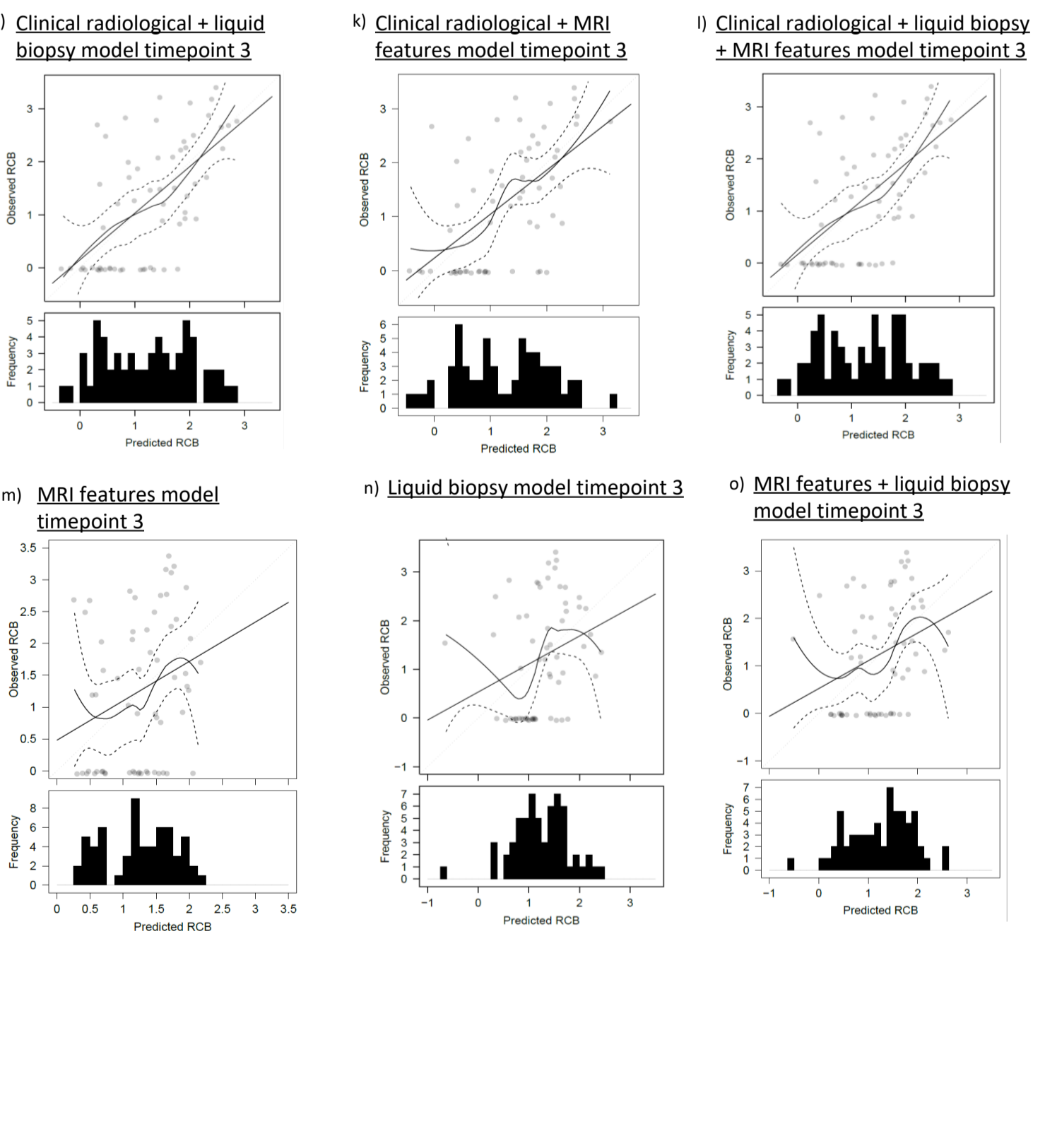
Supplementary figure 3

Calibration plots of models at timepoint 1 (a), timepoint 2 (b, d-i) and timepoint 3 (c, j-o)



Supplementary figure 3 (continued)

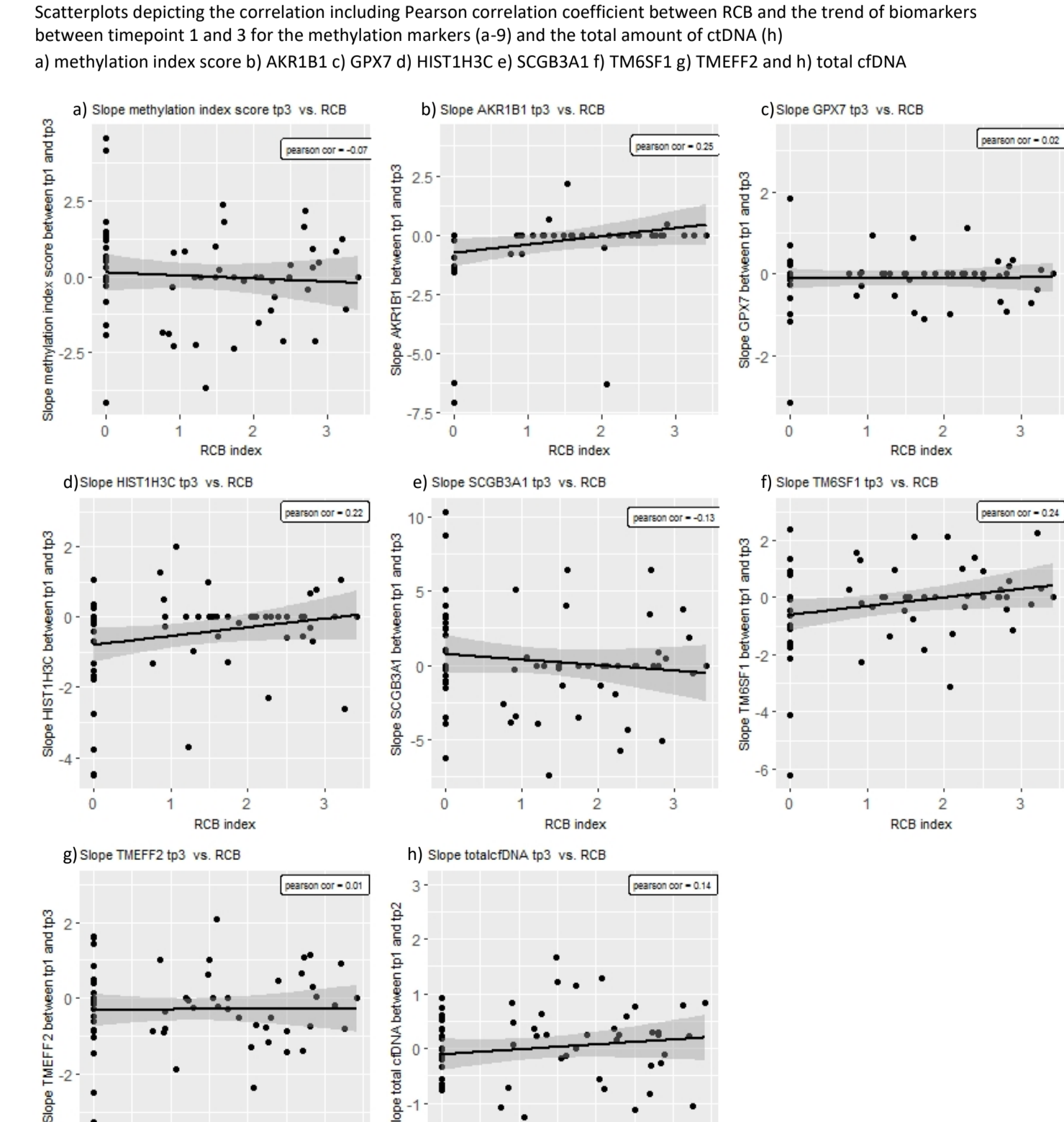
Calibration plots of models at timepoint 1 (a), timepoint 2 (b, d-i) and timepoint 3 (c, j-o)



Supplementary figure 4

Scatterplots depicting the correlation including Pearson correlation coefficient between RCB and the trend of biomarkers between timepoint 1 and 3 for the methylation markers (a-g) and the total amount of ctDNA (h)

a) methylation index score b) AKR1B1 c) GPX7 d) HIST1H3C e) SCGB3A1 f) TM6SF1 g) TMEFF2 and h) total ctDNA



Supplementary Table 1: ctDNA alterations detected

Alteration*	Number of times it was detected**
ESR1:pV392I	1
PIK3CA:pE542K	1
PIK3CA:pE545K	2
TP53:pR273H	2
TP53:pY220C	3
TP53:pR175H	1
ERBB2 amplification***	5

*The PIK3CA mutations were detected by both the UltraSEEK and naica Crystal Digital PCR technologies

**None of the alterations were detected in more than one sample of the same patient

*** ERBB2 amplification was not found in all patients in HER2+ disease on IHC

Supplementary Table 2: Summary of model performance corrected for optimism by leave one out cross validation including naive confidence intervals.

Model	Pre-treatment		On-treatment		Post-treatment	
	AUC (95% CI)	MSE (95% CI)	AUC (95% CI)	MSE (95% CI)	AUC (95% CI)	MSE (95% CI)
Clinical-radiological	0.76 (0.62-0.88)	0.94 (0.63-1.33)	0.83 (0.71-0.93)	0.86 (0.60-1.16)	0.82 (0.71-0.92)	0.87 (0.61-1.18)
Liquid biopsies	NA	NA	0.51 (0.34-0.67)	1.57 (1.22-1.98)	0.76 (0.63-0.88)	1.27 (1.00-1.60)
MRI features	NA	NA	0.66 (0.51-0.81)	1.27 (0.92-1.66)	0.69 (0.53-0.81)	1.25 (0.93-1.60)
Clinical-radiological + liquid biopsies	0.77 (0.64-0.88)	0.99 (0.63-1.42)	0.82 (0.71-0.92)	0.88 (0.58-1.18)	0.86 (0.76-0.94)	0.82 (0.54-1.12)
Clinical-radiological + MRI features	0.77 (0.64-0.88)	0.99 (0.65-1.41)	0.82 (0.70-0.92)	0.88 (0.57-1.23)	0.83 (0.70-0.93)	0.89 (0.56-1.24)
Liquid biopsies + MRI features	NA	NA	0.64 (0.47-0.78)	1.38 (1.01-1.83)	0.76 (0.64-0.88)	1.24 (0.92-1.57)
Clinical-radiological + Liquid biopsies + MRI features	0.76 (0.63-0.88)	1.03 (0.67-1.46)	0.81 (0.70-0.91)	0.91 (0.59-1.25)	0.86 (0.75-0.94)	0.84 (0.56-1.16)
Only clinical	0.76 (0.62-0.87)	0.94 (0.62-1.36)	0.76 (0.62-0.87)	0.94 (0.62-1.36)	0.76 (0.62-0.87)	0.94 (0.62-1.36)
Only clinical + liquid biopsies	0.76 (0.63-0.87)	0.98 (0.62, 1.42)	0.78 (0.65-0.88)	0.98 (0.67-1.39)	0.85 (0.74-0.94)	0.89 (0.58-1.29)
Only clinical + MRI features	0.76 (0.63-0.87)	0.98 (0.63-1.39)	0.82 (0.71-0.91)	0.92 (0.57- 1.41)	0.84 (0.72-0.93)	0.95 (0.59- 1.42)
Only clinical + MRI features + liquid biopsies	0.76 (0.63-0.87)	1.01 (0.65-1.43)	0.81 (0.70-0.91)	0.97 (0.62-1.45)	0.85 (0.74-0.93)	0.91 (0.57-1.35)

CI = confidence interval, AUC = area under the receiver operating characteristic curve for predicting pCR (RCB 0), MSE = mean standard error, measures the average squared difference between the observed and predicted values. A lower value indicates a better fit of the model. NA = not applicable, no predictors remained in the model.

Supplementary Table 3: Coefficients of prediction models

Model	Predictor	Coefficient
Clinical-radiological pre-treatment	(Intercept)	1.50
	IHC subtype ER-/HER2-	-0.76
	IHC subtype ER+/-/HER2+	-0.74
	Grade 3	-0.54
	Tumor size on baseline MRI	0
	Nodal status	0.89
	(Intercept)	0.84

Clinical-radiological on-treatment	IHC subtype ER-/HER2-	-0.56
	IHC subtype ER+/-/HER2+	-0.58
	Grade 3	-0.45
	Tumor size on baseline MRI	0
	Nodal status	0.71
	Relative change in tumor size on MRI 2 compared to baseline	0.01
Clinical-radiological post-treatment	(Intercept)	0.83
	IHC subtype ER-/HER2-	-0.54
	IHC subtype ER+/-/HER2+	-0.55
	Grade 3	-0.45
	Tumor size on baseline MRI	0
	Nodal status	0.70
	Relative change in tumor size on MRI 2 compared to baseline	0.01
	Relative change in tumor size on MRI 3 compared to baseline	0
Liquid biopsies pre-treatment	(Intercept)	1.25
	Amplifiable copies	0
	cfDNA integrity	0
	Methylation scores	0
	Mutations	0
	Plasma DNA concentration	0
MRI features pre-treatment	(Intercept)	1.25
	ADC	0
	Diameter	0
	Heterogeneity	0
	Kinetics	0
	Margin	0
	Shape	0
	T2	0
	Uptake	0
	Volume	0
Liquid biopsies on-treatment	(Intercept)	0
	Amplifiable copies	1.00
	cfDNA integrity	0
	Methylation scores	0
	Mutations	0
	Plasma DNA concentration	0
MRI features on-treatment	(Intercept)	0.12
	ADC	0
	Diameter	0

	Heterogeneity	0
	Kinetics	0
	Margin	0
	Shape	0
	T2	0
	Uptake	0
	Volume	0.90
Liquid biopsies post-treatment	(Intercept)	-2.82
	Amplifiable copies	1.15
	cfDNA integrity	0
	Methylation	2.10
	Mutations	0
	Plasma DNA concentration	0
MRI features post-treatment	(Intercept)	-0.33
	ADC	0
	Diameter	0.10
	Heterogeneity	0
	Kinetics	0
	Margin	0
	Shape	0
	T2	0.39
	Uptake	0
	Volume	0.78
Clinical-radiological + liquid biopsies pre-treatment	(Intercept)	-0.15
	Clinical-radiological model	1.12
	Liquid biopsies model	0
Clinical radiological + MRI features pre-treatment	(Intercept)	-0.15
	Clinical-radiological model	1.12
	Computer extracted MRI features model	0
Clinical radiological + LB + MRI features pre-treatment	(Intercept)	-0.15
	Clinical-radiological model	1.12
	Liquid biopsies model	0
	Computer extracted MRI features model	0
Clinical radiological + liquid biopsies on-treatment	(Intercept)	-0.65
	Clinical-radiological model	1.08
	Liquid biopsies model	0.44
Clinical radiological + MRI features on-treatment	(Intercept)	-0.50
	Clinical-radiological model	1.02
	Computer extracted MRI features model	0.38

Liquid biopsies + MRI features on-treatment	(Intercept)	-0.91
	Liquid biopsies model	0.62
	Computer extracted MRI features model	1.11
Clinical radiological + liquid biopsies + MRI features on-treatment	(Intercept)	-0.86
	Clinical-radiological model	0.98
	Liquid biopsies model	0.39
	Computer extracted MRI features model	0.32
Clinical radiological + liquid biopsies post-treatment	(Intercept)	-0.67
	Clinical-radiological model	0.98
	Liquid biopsies model	0.55
Clinical radiological + MRI features post-treatment	(Intercept)	-0.45
	Clinical-radiological model	1.03
	Computer extracted MRI features model	0.33
Liquid biopsies + MRI features post-treatment	(Intercept)	-0.47
	Liquid biopsies model	0.67
	Computer extracted MRI features model	0.71
Clinical radiological + liquid biopsies + MRI features post-treatment	(Intercept)	-0.55
	Clinical-radiological model	0.94
	Liquid biopsies model	0.50
	Computer extracted MRI features model	0
Only clinical model	(Intercept)	1.55
	IHC subtype ER-/HER2-	-0.85
	IHC subtype ER+/-/HER2+	-0.88
	Grade 3	-0.59
	Nodal status	0.96
Only clinical + liquid biopsies pre-treatment	(Intercept)	-0.02
	Only clinical model	1.02
	Liquid biopsies model	0
Only clinical + MRI features pre-treatment	(Intercept)	-0.02
	Only clinical model	1.02
	Computer extracted MRI features model	0
Only clinical + MRI features + liquid biopsies pre-treatment	(Intercept)	-0.02
	Only clinical model	1.02
	Liquid biopsies model	0
	Computer extracted MRI features model	0
Only clinical + liquid biopsies on-treatment	(Intercept)	-0.61
	Only clinical model	0.93
	Liquid biopsies model	0.55

Only clinical + MRI features on-treatment	(Intercept)	-0.75
	Only clinical model	0.83
	Computer extracted MRI features model	0.76
Only clinical + MRI features + liquid biopsies on-treatment	(Intercept)	-1.08
	Only clinical model	0.80
	Liquid biopsies model	0.39
	Computer extracted MRI features model	0.68
Only clinical + liquid biopsies post-treatment	(Intercept)	-0.62
	Only clinical model	0.82
	Liquid biopsies model	0.67
Only clinical + MRI features post-treatment	(Intercept)	-0.59
	Only clinical model	0.82
	Computer extracted MRI features model	0.66
Only clinical + MRI features + liquid biopsies post-treatment	(Intercept)	-0.81
	Only clinical model	0.76
	Liquid biopsies model	0.53
	Computer extracted MRI features model	0.36