

Supplementary Material

Table S1. Overview of the studies on predictive value of circulating biomarker in LARC.

Study articles								
authors	study year	number of patients	treatment type	radiation dosage	time to surgery	blood sampling time	measured biomarker	tumor response endpoint
Yang <i>et al.</i> [1]	2000-2009	137	5-FU based CRT	45Gy	3.4-12.4 weeks	<i>pre</i> -CRT/ <i>post</i> -CRT	CEA	pCR
Kim <i>et al.</i> [2]	2003-2011	314	5-FU based CRT	45-50Gy	6-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	CEA / CA 19-9 / thrombocytes	TRG (Dworak)
Choi <i>et al.</i> [3]	2007-2012	53	5-FU based CRT	45-63Gy	6-8 weeks	<i>pre</i> -CRT	CEA / Hb	pCR
Heo <i>et al.</i> [4]	2010-2013	52	5-FU based CRT	44-45Gy	4-8 weeks	<i>pre</i> -CRT / during-CRT / <i>post</i> -CRT	leukocytes / lymphocytes / Hb / CEA	pCR
Jung <i>et al.</i> [5]	2005-2013	984	5-FU based CRT	45-50Gy	6-8 weeks	<i>pre</i> -CRT	NLR / PLR / LMR	TRG (Gastrointestinal Pathology Study Group of the Korean Society of Pathologists)
Yang <i>et al.</i> [6]	2014-2017	531	n/a	N/A	5-12 weeks	<i>Pre</i> -CRT / <i>post</i> -CRT	CEA / CA19-9 / Hb	pCR
Cheong <i>et al.</i> [7]	2011-2017	145	5-FU based CRT	50.4Gy	6-8 weeks	<i>Pre</i> -CRT / <i>post</i> -CRT	CEA / NLR / PLR	TRG (AJCC)
Engel <i>et al.</i> [8]	2010-2018	331	5-FU or Capecitabine based CRT	45-50.4Gy	1-70 weeks	<i>pre</i> -CRT	CEA	pCR
Huang <i>et al.</i> [9]	2011-2017	236	5-FU based CRT	45-50.4Gy	n/a	<i>pre</i> -CRT / <i>post</i> -CRT	CEA / leukocytes / Hb	pCR (ypT0N0)
Gago <i>et al.</i> [10]	2012-2017	89	5-FU based CRT	45Gy	n/a	<i>pre</i> -CRT	CEA	TRG (Mandard)
Guo <i>et al.</i> [11]	2007-2018	751	Capectiabine based CRT	46-50Gy	6-8 weeks	<i>pre</i> -CRT	Serum lipids: apoAI, CEA, CA 19-9, TC, TG, HDL-c, LDL-c, apoB	TRG (Mandard)
Zhang <i>et al.</i> [12]	2008-2018	432	Capectiabine based CRT	50Gy	6-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	CEA	pCR
Berardi <i>et al.</i> [13]	1996-2003	317	5-FU based CRT or RT alone	n/a	4-6 weeks	<i>pre</i> -CRT, <i>post</i> -CRT <i>post</i> -Surgery	Hb	Downstaging
Song <i>et al.</i> [14]	2007-2016	674	5-FU or Capecitabine based CRT	45-50.4 Gy	6-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	CEA / CA 19-9	Downstaging / pCR
Yeo <i>et al.</i> [15]	2009-2013	260	5-FU or Capecitabine based CRT	45 Gy	n/a	<i>pre</i> -CRT	CEA / CA 19-9 / Hb	Downstaging / pCR
Restivo <i>et al.</i> [16]	1995-2010	260	5-FU or Capecitabine based CRT	45 Gy	minimum 4 weeks	<i>post</i> -CRT	CEA	pCR
Jang <i>et al.</i> [17]	2004-2009	109	5-FU or Capecitabine based CRT	45 Gy	6-9 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	CEA / Hb	TRG (Dworak)
Cai <i>et al.</i> [18]	2010-2017	284	5-FU or Capecitabine based CRT	46-50.4Gy	n/a	<i>pre</i> -CRT/ <i>post</i> -CRT	CEA / CA 19-9	TRG (NCCN) / Downstaging
Hu <i>et al.</i> [19]	2014-2015	149	5-FU or Capecitabine based CRT	46-50.4Gy	n/a	<i>pre</i> -CRT/ during-CRT/ <i>post</i> CRT	CEA	pCR / TRG
Kitayama <i>et al.</i> [20]	2004-2009	73	5-FU based CRT	50.4 Gy	n/a	<i>Pre</i> -CRT / <i>Post</i> -CRT	CEA / thrombocytes / lymphocytes	pCR
Sawada <i>et al.</i> [21]	2005-2014	267	5-FU based CRT	45-50.4 Gy	n/a	<i>pre</i> -CRT	CEA / LCR/LMR/NLR/PNI/ CRP to albumin ratio?/ NxCRP/MxCRP/NAR/NxM	TRG (Dworak)

Tawfik <i>et al.</i> [22]	2000-2015	98	5-FU based CRT	45-50Gy	n/a	<i>pre</i> -CRT / <i>post</i> -CRT	LMR/PLR/NLR/NAR / albumin/ CEA / Hb / thrombocytes / WBC	pCR
Krauthamer <i>et al.</i> [23]	2002-2007	140	5-FU based CRT	44Gy	6-8 weeks	<i>pre</i> -CRT	Albumin /Hb / NLR / Thrombocytes	pCR
Aires <i>et al.</i> [24]	2013-2019	171	5-FU or Capecitabine based CRT	45-55Gy	n/a	<i>pre</i> -CRT	CRP / CEA / CA 19-9 / Hb / Thrombocytes / NLR	TRG (Ryan)
Dreyer <i>et al.</i> [25]	1999-2010	79	5-FU or Capecitabine based CRT	39.6-50Gy	n/a	<i>pre</i> -CRT	mGPS / CEA / Hb / NLR / PLR	TRG (Rödel)
Agostini <i>et al.</i> [26]	1998-2008	67	5-FU based CRT	50Gy	4-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	cfDNA	TRG (Mandard)
Zitt <i>et al.</i> [27]	N/A	26	5-FU based CRT	45Gy	n/a	<i>Pre</i> -CRT/ <i>post</i> -CRT/ <i>post</i> -Surgery	cfDNA	yp Stage
Sun <i>et al.</i> [28]	N/A	34	Capecitabine based CRT	50Gy	6-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	cfDNA / KRAS mutation / MGMT promoter metyhlation	TRG (Dworak)
Carpinetti <i>et al.</i> [29]	N/A	4	5-FU based CRT	50.4-54Gy	n/a	<i>pre</i> -CRT / during-CRT / <i>post</i> -CRT	ctDNA	TRG (Dworak)
Sclafani <i>et al.</i> [30]	N/A	97	Capecitabine based CRT	50.4Gy	4-6 weeks	<i>pre</i> -CRT	ctDNA / KRAS and BRAF mutation	CR (Recist 1.1)
Tie <i>et al.</i> [31]	2012-2015	159	5-FU based CRT	n/a	n/a	<i>pre</i> -CRT / <i>post</i> -CRT / <i>post</i> -Surgery	ctDNA	TRG (Dworak)
Shalaby <i>et al.</i> [32]	N/A	93	Capecitabine based CRT	50.4Gy	6 weeks	<i>pre</i> -CRT	cfDNA, MGMT / ERCC 1 promoter methylation	TRG (Dworak)
Schou <i>et al.</i> [33]	2009-2014	123	Capecitabine based CRT	54Gy	6-8 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	cfDNA	pCR
Appelt <i>et al.</i> [34]	2005-2008	146	5-FU based CRT	50.4Gy	8 weeks	<i>pre</i> -CRT	methylation of NPY gene in ctDNA	TRG (Mandard)
Khakoo <i>et al.</i> [35]	2015-2016	47	Capecitabine based CRT	50.4-54Gy	n/a	<i>pre</i> -CRT / during CRT / <i>post</i> -CRT	ctDNA	mrTRG (MRI) or TRG (Mandard)
Pazdirek <i>et al.</i> [36]	2013-2017	36	Capecitabine based CRT	50.4Gy	8-10 weeks	<i>pre</i> -CRT / <i>post</i> -CRT	ctDNA	TRG (dworak)
Murahashi <i>et al.</i> [37]	2017-2018	85	5FU or Capecitabine based CRT	50.4Gy or 25 Gy	n/a	<i>pre</i> -CRT / <i>post</i> -CRT / <i>post</i> -Surgery	ctDNA / CEA	TNM / TRG (Dworak)
Zhou <i>et al.</i> [38]	2017-2019	104	Capecitabine based CRT	45-50Gy	8 weeks	<i>pre</i> -CRT / during-CRT / <i>post</i> -CRT	ctDNA	TNM / TRG (CAP)
McDuff <i>et al.</i> [39]	2014-2018	29	5-FU based CRT	50.4Gy	n/a	<i>pre</i> -CRT / <i>post</i> -CRT	ctDNA	pCR
Wada <i>et al.</i> [40]		106	5-FU or capecitabine based CRT	45-50.4Gy	n/a	<i>pre</i> -CRT	miRNA / CEA	TRG (Mandard)
Azizian <i>et al.</i> [41]	2011-2012	42	5-FU based CRT	not specified	4 weeks	<i>pre</i> -CRT / during-CRT / <i>post</i> -CRT	miRNA	Lymph node negativity
D'Angelo <i>et al.</i> [42]	2007-2011	34	5-FU or Capecitabine based CRT	at least 45Gy	n/a	<i>pre</i> -CRT	miRNA	TRG (Mandard)
Hiyoshi <i>et al.</i> [43]	2013-2016	94	n/a	50.4Gy	4-8 weeks	<i>pre</i> -CRT	miRNA	TRG (Dworak)
Yu <i>et al.</i> [44]	2006-2015	87	n/a	50-50.4Gy	6-8 weeks	<i>pre</i> -CRT	miRNA	TRG (Mandard)
Meltzers <i>et al.</i> [45]	2013-2015	29	Capecitabine based CRT or SCRT	25 or 50 Gy	n/a	<i>pre</i> -CRT	Exosomal miRNA	TRG (CAP) or TRG (Bouzourene)
Baek <i>et al.</i> [46]	2012-2015	89	5-FU or Capecitabine based CRT	45-504Gy	6-8 weeks	<i>pre</i> -CRT	miRNA	TRG (Rödel)

Dreussi <i>et al.</i> [47]	N/A	265	5-FU based CRT	50.4-55Gy	n/a	n/a	SNP related to miRNA	pCR / TRG
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Legend : 5-FU : 5-fluorouracil, apoA1 : apolipoprotein A1, apoB : apolipoprotein B, CA 19-9 : carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, cfDNA : cell free DNA, ctDNA : circulating tumor DNA, CRT : chemoradiotherapy, CAP : college of american pathologists, CR : complete response, CRP : c-reactive protein, Hb : hemoglobin, HDL-c : high-density lipoprotein cholesterol, LDL-c : low-density lipoprotein cholesterol, LCR : lymphocyte to CRP ratio, LMR : lymphocyte to monocyte ratio, mrTRG : magnetic resonance tumor regression grade, miRNA : micro RNA, mGPS : modified Glasgow prognostic score, MxCRP : monocyte x CRP product NAR : neutrophil to albumin ratio, NLR : neutrophile to lymphocyte ratio, NxCRP : neutrophil x CRP product, NxM : neutrophile x monocyte product, n/a : not available, pCR : pathological complete response, PLR: latelet to lymphocyte ratio, SNP : single nucleotide polymorphism, TG : triglyceride, TC : total cholesterol, TRG: tumor regression grade.

Table S2. Studies exploring CA19-9 as a biomarker predictive of tumor regression following CRT.

Study	Cut-off	N	Measured outcome	Sn	Sp	VPP	VPN	p.value (Univariate)
<i>pre-CRT</i>								
Aires <i>et al.</i> [24]	3.5 U/ml	171	TRG 0-1 (Rayan)	39.6%	72.5%	n/a	n/a	ns
Yeo <i>et al.</i> [15]	9 U/ml	260	ypStage 0-1	70.2%	50%	44.3%	74.8%	<0.01(*)
	10 U/ml	260	ypStage 0-1	74.5%	48.2%	44.9%	76.9%	<0.01
Song <i>et al.</i> [14]	12.6 U/ml	674	Downstaging	62%	54.5%	52.9%	63.4%	0.0001
Guo <i>et al.</i> [11]	35 U/ml	751	TRG 1-2 (Mandard)	n/a	n/a	n/a	n/a	ns
Kim <i>et al.</i> [2]	37 U/ml	314	pCR	86.5%	21.5%	13.7%	91.7%	ns
Yang <i>et al.</i> [6]	37 U/ml	531	pCR	85%	24.8%	20.8%	87.7%	ns
Cai <i>et al.</i> [18]	37 U/ml	284	TRG 0-1 (NCCN)	93.6%	97.7%	39.6%	70.8%	ns
<i>post-CRT & pre-surgery</i>								
Song <i>et al.</i> [14]	11.3 U/ml	674	Downstaging	58%	49.1%	48.5%	58.6%	ns
<i>pre- and post CRT ratio</i>								
Song <i>et al.</i> [14]	0.92	674	pCR	44.9%	66.7%	25.4%	82.7%	0.012
	1.28	674	Downstaging	73.1%	41.7%	50.9%	65.3%	<0.0001(*)
<i>reduction ratio</i>								
Yang <i>et al.</i> [6]	n/a	531	pCR	n/a	n/a	n/a	n/a	ns

(*) : also significant in multivariate analysis. Legend : CRT : chemoradiotherapy, NCCN : national comprehensive cancer network, NPV : negative predictive value, ns : non-significant, n/a : not available, N : number of patients, pCR : pathological complete response, yp Stage : pathological stage after neo-adjuvant treatment, PPV : positive predictive value, Sn : sensitivity, Sp : specificity, TRG : tumor regression grade.

Table S3. Studies exploring hemoglobin level as a biomarker predictive of tumor regression following CRT.

Study	Cut-off	N	Measure outcome	Sn	Sp	VPP	VPN	p. value (Univariate)
<i>pre-CRT</i>								
Yang J. <i>et al.</i> [6]	9 g/dl	531	pCR	97%	5.6%	19.2%	88.9%	ns
Choi <i>et al.</i> [3]	10 g/dl	53	pCR	90.9%	14.3%	21.7%	85.7%	ns
Krauthamer <i>et al.</i> [23]	12 g/dl	140	pCR	63.6%	51%	36.8%	75.8%	ns
Berardi <i>et al.</i> [13]	12 g/dl	317	Downstaging	n/a	n/a	n/a	n/a	0.05
Aires <i>et al.</i> [24]	12.2g/dl	171	TRG 0-1 (Rayan)	81.4%	39.1%	n/a	n/a	0.0036
Yeo <i>et al.</i> [15]	12.5 g/dl	260	Yp Stage 0-1	59.8%	48.2%	39%	68.4%	ns
Heo <i>et al.</i> [4]	13.2 g/dl	52	pCR	35.7%	40.5%	18.5%	62.5%	ns
Jang <i>et al.</i> [17]	13.5 g/dl	109	TRG 3-4 (Dworak)	42.2%	54.7%	39.6%	57.4%	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	0.05
Dreyer <i>et al.</i> [25]	13 g/dl (M) 11.5 g/dl (F)	79	TRG 3-4 (Rödel)	64.7%	46.5%	48.9%	62.5%	ns
<i>during CRT</i>								
Huang <i>et al.</i> [9]	10 g/dl	236	pCR	83.9%	32.8%	28%	86.8%	0.0159(*)
<i>post-CRT & pre-surgery</i>								
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns

(*) : also significant in multivariate analysis. Legend : CRT : chemoradiotherapy, NPV : negative predictive value, ns : non-significant, n/a : not available, N : number of patients, pCR : pathological complete response, yp Stage : pathological stage after neo-adjuvant treatment, PPV : positive predictive value, Sn : sensitivity, Sp : specificity, TRG : tumor regression grade.

Table S4. Studies exploring albumin or CRP levels as biomarkers predictive of tumor regression following CRT.

[illegible]

Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
CRP								
<i>pre</i> -CRT								
Aires <i>et al.</i> [24]	3.5 mg/L	171	TRG 0-1 (Rayan)	54.8%	93.5%	n/a	n/a	<0.0001(*)
mGPS								
Dreyer <i>et al.</i> [25]	mGPS 0 (vs mGPS 1-2)	79	TRG 3-4 (Rödel)	88%	44.7%	51.1%	85%	0.022(*)

(*) : also significant in multivariate analysis. Legend : CRT : chemoradiotherapy, NPV : negative predictive value, ns : non-significant, n/a : not available, N : number of patients, pCR : pathological complete response, PPV : positive predictive value, Sn : sensitivity, Sp : specificity, TRG : tumor regression grade.

Table S5. Studies exploring leukocyte and lymphocyte counts as well as NLR, NAR, LMR and PLR ratios as biomarkers predictive of tumor regression following CRT.

Study	Cut-off	N	Measure outcome	Sn	Sp	VPP	VPN	p value (univariate)
leukocyte Count								
<i>pre</i> -CRT								
Heo <i>et al.</i> [4]	7.3 G/l	52	pCR	83.3%	45.7%	34.5%	88.9%	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
<i>post</i> -CRT <i>pre</i> -surgery								
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
during CRT								
Huang <i>et al.</i> [9]	3 G/l	236	pCR	51.8%	36.3%	20.3%	70.1%	ns
lymphocytes								
<i>pre</i> -CRT								
Kitayama <i>et al.</i> [20]	n/a	73	pCR	n/a	n/a	n/a	n/a	0.02(*)
Heo <i>et al.</i> [4]	1.996 G/l	52	pCR	42.9%	47.4%	23.1%	75%	ns
during treatment (<i>post</i> -4 weeks)								
Heo <i>et al.</i> [4]	X	52	pCR	42.9%	47.4%	23.1%	75%	ns
<i>post</i> -4 weeks lymphocytes/ <i>pre</i> -CRT lymphocytes ratio								
Heo <i>et al.</i> [4]	0.35	52	pCR	85.7%	57.9%	42.9%	91.7%	0.01(*)
during treatment (<i>post</i> -8 weeks)								
Heo <i>et al.</i> [4]	X	52	pCR	22.2%	64.3%	16.7%	72%	ns

post-8 weeks lymphocytes/pre-CRT lymphocytes ratio								
Heo <i>et al.</i> [4]	0.47	52	pCR	33.3%	53.6%	18.8%	71.4%	ns
during treatment (<i>post</i> -12 weeks)								
Heo <i>et al.</i> [4]	1.033 G/l	52	pCR	66.7%	26.1%	26.1%	66.7%	ns
post-12 weeks lymphocytes/pre-CRT lymphocytes ratio								
Heo <i>et al.</i> [4]	0.53	52	pCR	55.6%	47.8%	29.4%	73.3%	ns
neutrophil to lymphocyte ratio (NLR)								
pre-CRT								
Jung <i>et al.</i> [5]	1.7	984	TRG (total-near total)	47.2%	57.5%	44.7%	59.9%	ns
Aires <i>et al.</i> [24]	2.3	171	TRG 0-1 (Rayan)	51%	58%	n/a	n/a	ns
Cheong <i>et al.</i> [7]	2.8	145	pCR	n/a	n/a	n/a	n/a	0.013(*)
Krauthamer <i>et al.</i> [23]	5	140	pCR	77.3%	40.8%	37%	80%	ns
Dreyer <i>et al.</i> [25]	5	79	TRG 3-4 (Rödel)	91.4%	25%	49.2%	78.6%	ns
Sawada <i>et al.</i> [21]	n/a	267	TRG 3-4 (Dworak)	n/a	n/a	n/a	n/a	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	0.012
post-CRT								
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
neutrophil to albumin ratio (NAR)								
pre-CRT								
Sawada <i>et al.</i> [21]	n/a	267	TRG 3-4 (Dworak)	n/a	n/a	n/a	n/a	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	0.002(*)
post-CRT								
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	0.05
lymphocyte to monocyte ratio (LMR)								
pre-CRT								
Sawada <i>et al.</i> [21]	n/a	267	TRG 3-4 (Dworak)	n/a	n/a	n/a	n/a	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
Jung <i>et al.</i> [5]	6.8	984	TRG (total-near total)	12.2%	86.3%	44.7%	58.2%	ns
post-CRT pre-Surgery								

Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
platelet to lymphocyte ratio (PLR)								
<i>pre-CRT</i>								
Jung <i>et al.</i> [5]	92.88	984	TRG (total-near total)	20.2%	75.7%	37.8%	56.6%	ns
Cheong <i>et al.</i> [7]	138.2	145	pCR	n/a	n/a	n/a	n/a	n/a
Dreyer <i>et al.</i> [25]	300	79	TRG 3-4 (Rödel)	88.6%	27.3%	49.2%	75%	ns
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
<i>post-CRT</i>								
Tawfik <i>et al.</i> [22]	n/a	98	pCR	n/a	n/a	n/a	n/a	ns
neutrophil and monocyte product (N x M) <i>pre-CRT</i>								
Sawada <i>et al.</i> [21]	1,440,000	267	TRG 3-4 (Dworak)	n/a	n/a	n/a	n/a	0.001(*)
lymphocyte to CRP ratio (LCR) (<i>pre-CRT</i>)								
Sawada <i>et al.</i> [21]	18.141	267	TRG 3-4 (Dworak)	n/a	n/a	n/a	n/a	0.007(*)

(*) : also significant in multivariate analysis. Legend : CRT : chemoradiotherapy, NPV : negative predictive value, ns : non-significant, n/a : not available, N : number of patients, pCR : pathological complete response, PPV : positive predictive value, Sn : sensitivity, Sp : specificity, TRG : tumor regression grade.

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