Supplementary methods

Patients, data extraction, and end points

Inclusion criteria were biopsy-confirmed adenocarcinoma of the colon or rectum and first line palliative treatment with CAPEOXBEV or CAPEOX. Exclusion criteria were other coexisting malignancy or endocrine histology. Patients in the CAPEOX cohort were also not allowed to have been treated with BEV in later lines. The ten departments of oncology from which we included patients encompassed all of the departments in the country which identified CAPEOXBEV as one of their preferred first line treatments for patients with mCRC. The randomized study from which we partly included our control cohort was a study of chronomodulated versus standard-dosing of CAPEOX, i.e. all patients received CAPEOX in the same dose [1]. Treatment was given as infusional oxaliplatin 130 mg/m^2 on day 1, capecitabine 2000 mg/m^2 daily days 1–14, +/- infusional bevacizumab 7.5 mg/kg on day 1, repeated every 3 weeks.

Data were extracted from individual patient records and electronic databases at each hospital using a standardized case report form. Pathology data and survival status were extracted from national databases using the unique Civil Registration System number assigned to every Danish citizen.

Disease evaluation was done every three to four cycles using computed tomography (CT) scans and the Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 criteria [2]. Date of disease progression was defined as the date of an evaluation CT scan showing progression according to the RECIST 1.0 criteria or, in a few cases, by other clinical signs of progression, if a diagnosis of clinical progression was stated unequivocally in the patient record. The end point time to disease progression (TTP) was measured from initiation of treatment to disease progression. If patients died without evidence of disease progression they were censored at the last known date of non-

progression. If patients died without having any disease evaluations they were excluded from the TTP analyses.

Primary tumor location was registered as 1: cecum and ascending colon, 2: right flexure and transverse colon, 3: left flexure and descending colon, 4: sigmoid- and rectosigmoid colon, or 5: rectum.

More than 98% of patients were White.

MiRNA expression analysis

Briefly, the procedure utilized for the miRNeasy FFPE kit RNA purification was as follows. Samples were deparaffinized and then lysed with proteinase K digestion followed by heat treatment. After centrifugation, the supernatant was recovered and treated with DNase. After mixing with buffer and ethanol, part of the mixture was transferred to an RNeasy MinElute spin column where total RNA was bound. After washing, the RNA was eluted and normalized to 70 ng/µl either manually (screening cohort) or using an automated procedure (validation and control cohorts).

The purity and concentration of RNA was assessed by absorbance spectrometry on a NanoDrop 8000 (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Samples with a 260nm/280nm-ratio below 1.8 were discarded and new sections from the corresponding tissue block were cut and purified.

Samples were stored at -80 °C until they were used for miRNA expression analysis.

The procedure utilized for the Applied Biosystems Human LDA Card Set array analyses was as follows. RNA was transcribed into cDNA in 2 multiplex reactions each containing 3 µl of the small

RNA preparation, corresponding to 200 ng total RNA, and either Megaplex RT Primer Pool A or Pool B, and using the TaqMan® MicroRNA Reverse Transcription Kit in a total reaction volume of 16 µl. Prior to loading the arrays, a 12-cycle pre-amplification reaction was performed using 2.5 µl cDNA in a 25-µl reaction and using Megaplex PreAmp Primers Pool A or B. Each of the arrays was loaded with 1/50 of the preamplification reaction which was mixed with TaqMan Gene Expression Master Mix in a total reaction volume of 800 µl and run on the 7900HT Fast Real-Time PCR System.

The same procedures were executed for the custom LDA card as for the large array, except for 8 different samples being loaded onto each card instead of one.

MiRNA in situ hybridization

Sequence and melting temperature for the targeted probes were as follows.

miR-185-5p *(*TCAGGAACTGCCTTTCTCTCCA, RNA T_m 85°C*),*

miR-449a *(*ACCAGCTAACAATACACTGCCA, RNA T_m 82°C*),*

miR-455-5p (CGATGTAGTCCAAAGGCACATA, RNA T_m 83°C*),*

miR-592 (ACATCATCGCATATTGACACAA, RNA T_m 84°C*),*

miR-664-3p (TGTAGGCTGGGGATAAATGAATA, RNA T_m 81°C*),*

miR-21-5p *(*TCAACATCAGTCTGATAAGCTA, RNA T_m 83°C*),* and

miR-126-3p (CATTATTACTCACGGTACGA, RNA T_m 84°C).

A 22-mer scrambled LNA probe with a random sequence (TGTAACACGTCTATACGCCCA, RNA T_m 87°C) was included as a negative control. All LNA oligos were 5, 6-carboxyfluorescein

(FAM)-labeled at both the 5'- and 3'-ends. Briefly, 6 µm thick tissue sections were mounted on glass slides and deparaffinized and then placed in a Tecan Freedom Evo automated hybridization instrument *(*Tecan, Männedorf, Switzerland*)* in which the following steps were performed: proteinase-K treatment (25 µg/ml at 37°C for 8 min.), pre-hybridization (at 57°C for 15 min.), hybridization with FAM-labeled LNA probes (40 nM/ml probe at 57°C for 60 min.), stringent washes with SSC buffers (at 57°C for at least 33 min.), blocking reagent (PBS containing 2% Sheep serum, 1% BSA and 0.05% Tween-20), alkaline phosphatase-conjugated anti-FAM, enzymatic development that precipitates the blue NBT-BCIP substrate, and nuclear fast red counterstain. The sections were finally dehydrated and mounted. All LNA probes were HPLC purified.

In total, twenty patient samples were studied using ISH.

Statistical analysis

Differences in characteristics between cohorts were tested using Wilcoxon Mann-Whitney test for continuous variables, Fisher's exact test for categorical variables, and log rank test for time to event variables.

Screening study

The C_ts (before subtracting from 40) were adjusted according to the spike-in miRNA value (ath-miR-159a). That is, for each C_t-value in a given subject we subtract 0.28 × (spike-in - 22) from the C_t-value, since the spike-in is supposed to be approximately 22 (data not shown).

The calculations relating miRNA expression to outcome were done for both raw-, quantile-normalized [3] and mean-normalized data sets. The number of missing values within each miRNA was counted before the normalization. If certain miRNAs had more than 45% missing values they were removed in the quantile-normalized data set, because of the normalization function's

requirements. Mean-normalization was performed by subtracting the mean of the 120 miRNAs with the lowest mean C_t from the C_t of all miRNAs. This is done sample-wise.

Both $P < 0.001$ and a threshold found by cross validation [4] were used for selecting which miRNAs to include in the multivariate analyses.

The criteria used for selecting miRNAs from the screening study for further investigation were:

1. Retained in multivariate models after backwards selection using at least 2 types of expression data (raw, quantile-normalized, mean-normalized) for TTP or OS
2. OR retained in a multivariate model after backwards selection using 1 type of expression data for TTP or OS and within the top 35 most significantly correlated to TTP or OS using both raw- and quantile-normalized expression data
3. OR within the top 5 most significantly correlated to TTP or OS univariately using both raw- and quantile-normalized expression data

The confidence intervals in the unadjusted analyses that are shown in Figure 1 and 2 and in Figure S2 and S3 were computed using BCa bootstrapping [5] with R=999 bootstrap replications.

Table S1. MiRNAs retained in one or more multivariate models after backwards selection or top-5 most significant univariately

		Multivariate model in which a given miRNA was retained – by end point and data type									
		TTP					OS				
MiRNA name[a]	Mature miRNA sequence[a]	Raw	Raw CV	Quan	Quan CV	Mean	Raw	Raw CV	Quan	Quan CV	Mean
hsa-miR-1	UGGAAUGUAAAGAAGUAUGUAU					x					
hsa-miR-15a-5p	UAGCAGCACAUAAUGGUUUGUG								x	x	
hsa-miR-17-3p	ACUGCAGUGAAGGCACUUGUAG				x	x					
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	x	x			x				x	
hsa-miR-29a-5p[b]	ACUGAUUUCUUUUGGUGUUCAG					x					
hsa-miR-29b-3p	UAGCACCAUUUGAAAUCAGUGUU	x	x			x		x			x
hsa-miR-145-3p	GGAUUCCUGGAAAUACUGUUCU	x	x	x	x						
hsa-miR-148a-3p[b]	UCAGUGCACUACAGAACUUUGU								x	x	
hsa-miR-155-5p	UUAAUGCUAAUCGUGAUAGGGGU								x		
hsa-miR-181a-5p[b]	AACAUUCAACGCUGUCGGUGAGU							x			
hsa-miR-185-5p	UGGAGAGAAAGGCAGUUCCUGA			x							
hsa-miR-193b-5p	CGGGGUUUUGAGGGCGAGAUGA	x	x	x	x	x					
hsa-miR-196b-5p	UAGGUAGUUUCCUGUUGUUGGG						x	x		x	x
hsa-miR-204-5p	UUCCCUUUGUCAUCCUAUGCCU				x	x			x	x	x
hsa-miR-214-5p	UGCCUGUCUACACUUGCUGUGC					x					x
hsa-miR-338-3p	UCCAGCAUCAGUGAUUUUGUUG								x		
hsa-miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG		x				x	x	x	x	
hsa-miR-449a	UGGCAGUGUAUUGUUAGCUGGU									x	x
hsa-miR-449b-5p[b]	AGGCAGUGUAUUGUUAGCUGGC								x		
hsa-miR-455-5p	UAUGUGCCUUUGGACUACAUCG							x			
hsa-miR-497-5p	CAGCAGCACACUGUGGUUUGU					x					
hsa-miR-501-5p	AAUCCUUUGUCCCUGGGUGAGA					x					
hsa-miR-545-3p	UCAGCAAACAUUUAUUGUGUGC								x	x	x
hsa-miR-552-3p	AACAGGUGACUGGUUAGACAA								x		x
hsa-miR-592[c]	UUGUGUCAAUAUGCGAUGAUGU										
hsa-miR-664-3p	UAUUCAUUUAUCCCCAGCCUACA				x	x					

[a] www.mirbase.org, accessed October 22 2013

[b] These miRNAs were not selected for further study

[c] In univariate analyses, miR-592 was significantly correlated to OS with the second lowest p-value both using raw- and quantile-normalized expression

Abbreviations: TTP, time to disease progression; OS, overall survival; Raw, non-normalized raw values; HR, hazard ratio per inter-quartile range increase; Quan, quantile-normalized values; CV, threshold for inclusion determined by cross-validation (ref); mean, mean-normalized values

Table S2. Predicted targets and publications regarding identified miRNAs

miR-664-3p

Top 20 predicted target genes

ZNF423, CTD-2162K18.4, ***NLGN1,*** *C18orf34, PRTG, SLC10A2, C6orf106,* ***MDGA2,*** *EBF2, PLP2, IRF2, RSBN1, MYOG,* ***GPHN,*** *AHCTF1, KLF12, CT47A4, ZMYND11, CT47A8, CT47A10*

Publications

Cell/tissue type	Function/expression level	Author	Year
Hepatocellular carcinoma	Upregulated; targets MAT1A; increases tumor growth, invasion, and metastasis	Yang [6]	2013
Myocardial endothelial cells	**Upregulated in endothelial cells from diabetic mice with impaired angiogenesis**	**Wang [7]**	**2009**

miR-455-5p

Top 20 predicted target genes

GDAP2, EHD4, MYLIP, BRD1, KDSR, LYPD3, MOB4, SESN3, TMEM30A, ZNF385A, GABRB2, KCNJ2, NDUFAF4, SOCS3, MIPOL1, RPS6KB1, TAOK1, LUC7L3, ZFYVE26, SUZ12

Publications

Cell/tissue type	Function/expression level	Author	Year
Basal cell carcinoma	Upregulated	Sand [8]	2012
Endometrial cancer	Downregulated	Hiroki [9]	2010
Laryngeal cancer	Upregulated	Saito [10]	2013
Medullary thyroid carcinoma	Downregulated	Hudson [11]	2013
Murine cardiac myocytes	Downregulated by ATF6, which is activated by ischemic stress	Belmont [12]	2012
Murine macrophages	**Upregulated in response to *Candida albicans***	**Monk [13]**	**2010**
Skeletal muscle cells	**Upregulated by proinflammatory TWEAK cytokine**	**Panguluri [14]**	**2010**

miR-592

Top 20 predicted target genes

PAFAH1B1, AKAP6, ROCK1, LRRC4C, ATP5A1, C14orf102, CHGB, STX16, CAND1, PTPRD, ZSWIM6, NFIA, SCGB2A2, RP11-67H2.1, TTC29, KLHL29, EMR2, USP9X, CEACAM3, PRUNE2

Publications

Cell/tissue type	Function/expression level	Author	Year
Colorectal cancer	**Downregulated in dMMR and upregulated in pMMR (versus normal epithelium)**	**Sarver [15]**	**2009**
Colorectal cancer	**2.5-fold higher in cancer epithelium than cancer stroma**	**Nishida [16]**	**2012**
Colorectal cancer	**3.96-fold higher in left colon and rectum versus right colon**	**Schee [17]**	**2013**
Colorectal cancer	**Higher in patients with disease control versus progression as best response on treatment with anti-EGFR**	**Mosakhani [18]**	**2012**
Colorectal cancer	Upregulated in doxorubicin-resistant cell line	Qu [19]	2013
Hepatocellular carcinoma	Downregulated in HBV-associated HCC	Wang [20]	2012

miR-196b-5p

Top 20 predicted target genes

HOXA7, HOXC8, SLC9A6, WIPF2, HAND1, HOXA9, PSMD11, CASK, GATA6, HOXA5, CCDC47, BCAT1, LRP1B, CCNJ, NR6A1, VSNL1, ZBTB26, HOXB7, COL1A2, GDF3

Publications

Cell/tissue type	Function/expression level	Author	Year
Colorectal cancer	**Downregulated in dMMR and unchanged in pMMR (versus normal epithelium)**	**Sarver [15]**	**2009**
Colorectal cancer	**3.7-fold higher in cancer epithelium than cancer stroma**	**Nishida [16]**	**2012**
Rectal cancer	**Upregulated in cancers that responded to neo-adjuvant 5-fluorouracil and radiation**	**Svoboda [21]**	**2012**
Breast cancer	Inhibited HOXC8 and inhibited migration and metastases	Li [22]	2010
Cervical cancer	Downregulated; high expression associated with improved disease-free survival; targets *HOXB7*	How [23]	2013
Endometriotic cyst stromal cells	Overexpression lowered c-myc and Bcl-2 mRNA expression	Abe [24]	2013
Endothelial cells	Upregulated in tumor-associated Ecs; upregulated by VEGF treatment; suppression led to increased HOXD10; Suppression decreased EC profileration and migration	Plummer [25]	2013
Esophageal cancer	Upregulated in tumor from patient with good prognosis	Zhao [26]	2013
Esophageal cancer	Upregulated	Liu [27]	2013
Gastric cancer	Upregulated	Tsai [28]	2010
Gastric cancer	Downregulated by ETS2 and induces epithelial-mesenchymal transition	Liao [29]	2012
Gastric cancer	Upregulated	An [30]	2013
Gastric cancer	Upregulated; high expression was associated with poor survival; expression correlated positively with HOXA10 expression	Lim [31]	2013
Glioblastoma	Upregulated; high miR-196b-5p was associated with shorter survival	Guan [32]	2010
Glioblastoma	Upregulated; high miR-196b-5p was associated with longer survival	Lakomy [33]	2011
Glioblastoma	Overexpression increases proliferation; High miR-196b-5p was associated with shorter survival	Ma [34]	2012
Hepatocellular carcinoma	Upregulated	Shen [35]	2013
Leukemia	Upregulated; increases proliferation and decreases differentiation; associated with HOX-gene activation	Popovic [36]	2009
Leukemia	Downregulated; inhibited c-myc	Bhatia [37]	2010
Leukemia	Overexpression inhibited ERG transcription factor	Coskun [38]	2011
Leukemia	Targets both oncogenes HOXA9/MEIS1 and tumor suppressor gene FAS	Li [39]	2012
Leukemia	Downregulated	Bhatia [40]	2011
Leukemia	Downregulated; targets *HOXA9* and *ABL1*	Liu [41]	2013
Leukemia	High expression was associated with shorter overall survival	Diaz-Beyá [42]	2013
Osteosarcoma	Upregulated	Namløs [43]	2012
Pancreatic cancer	Upregulated	Yu [44]	2012
Pancreatic cancer	Upregulated	Schultz [45]	2012
Peripheral nerve s heath tumors	Upregulated in malignant versus benign lesions	Masliah-Planchon [46]	2013
Prostate cancer	Epigenetically downregulated	Hulf [47]	2011

Genes and publications in bold are discussed in the manuscript.

[a] Genes are ranked according to the most likely targets identified using the DIANA-microT-CDS (v5.0) algorithm (reference in manuscript)

[c] Three additional HOX genes are predicted as targets among the top 100 target (HOXB1, HOXB6, and HOXB7)

Abbreviations: MREs, miRNA recognition elements

Figure S1. CONSORT diagram

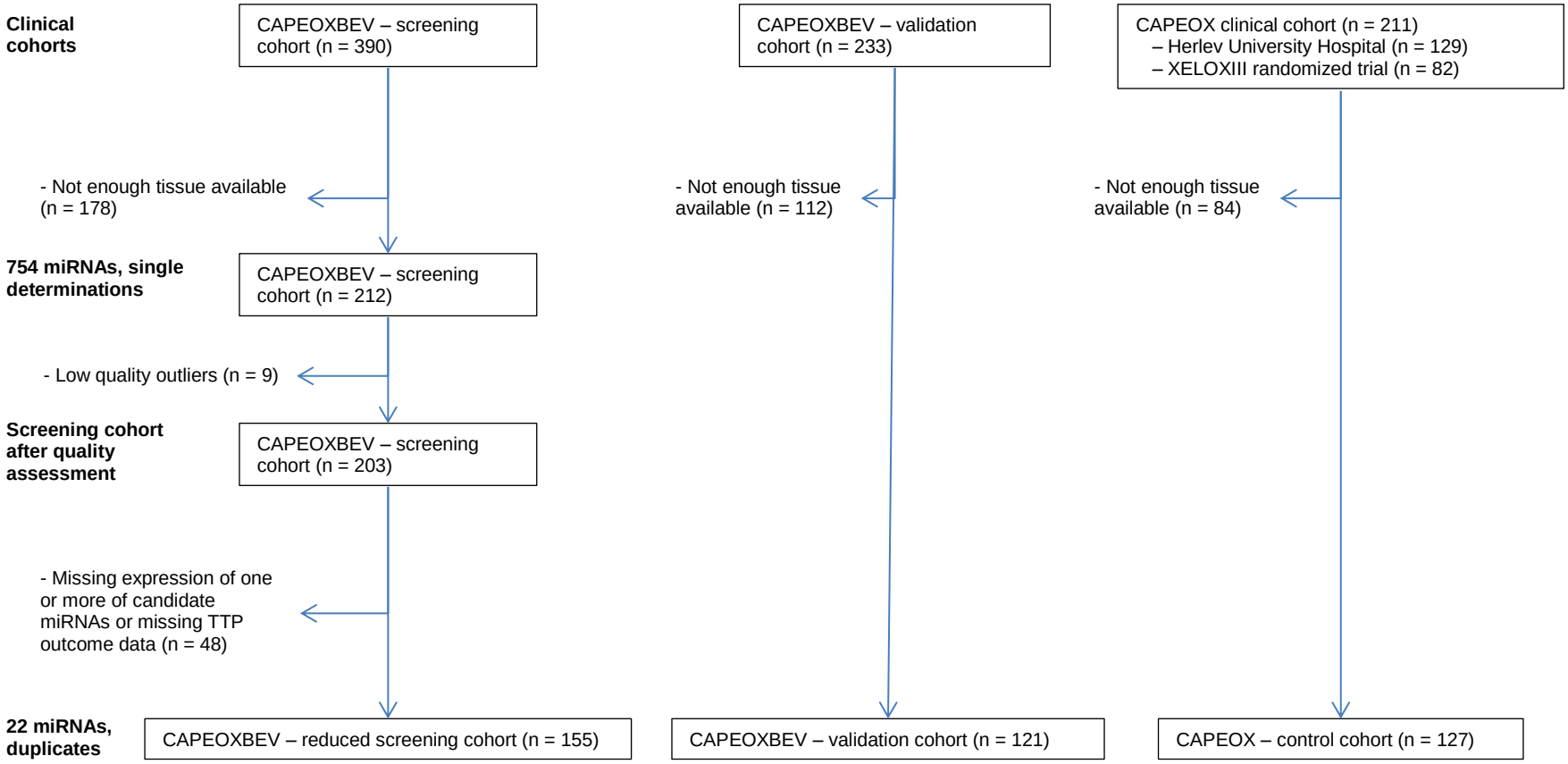
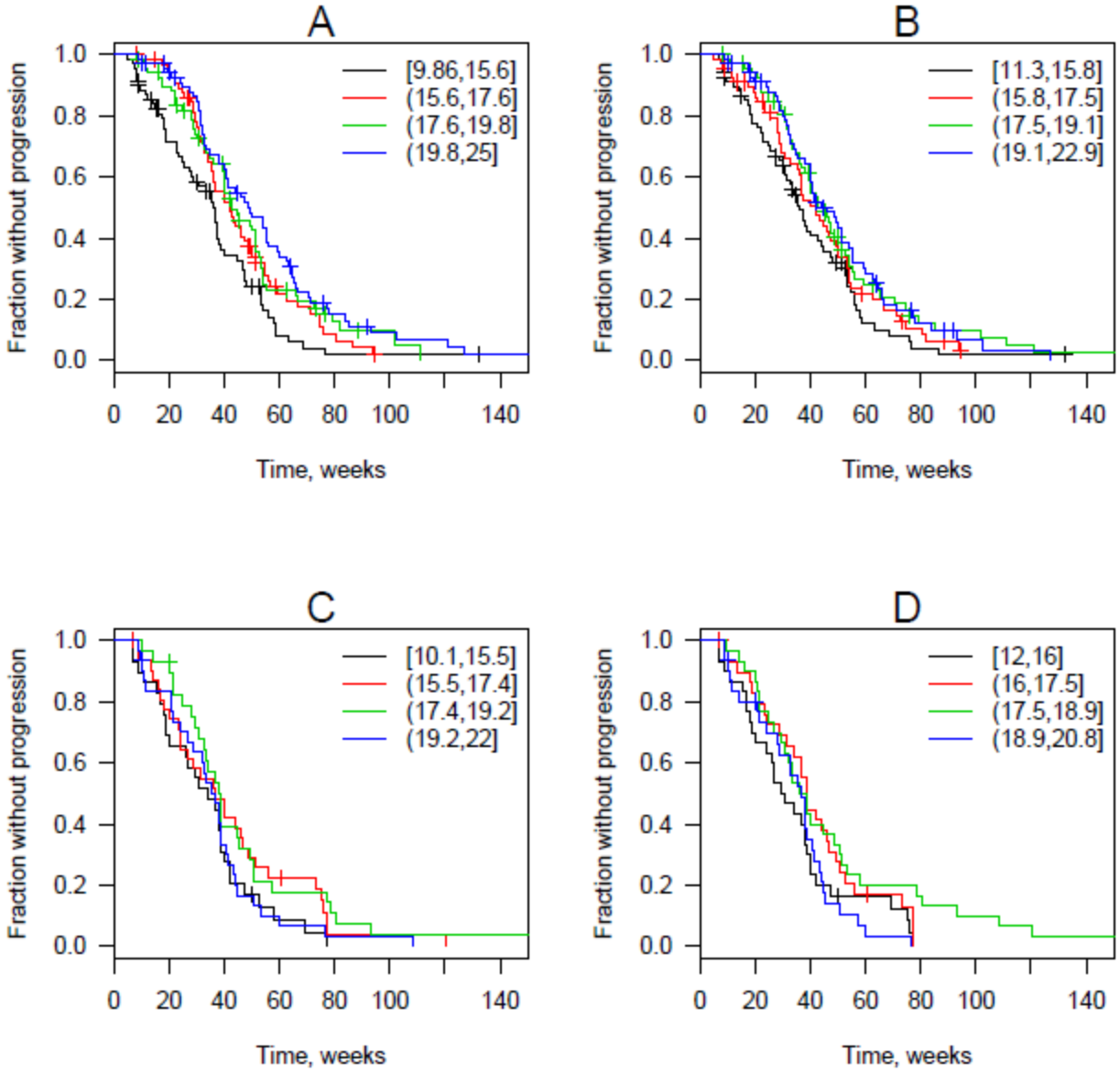


Figure S2. Time to disease progression according to quartiles of mir-664-3p expression

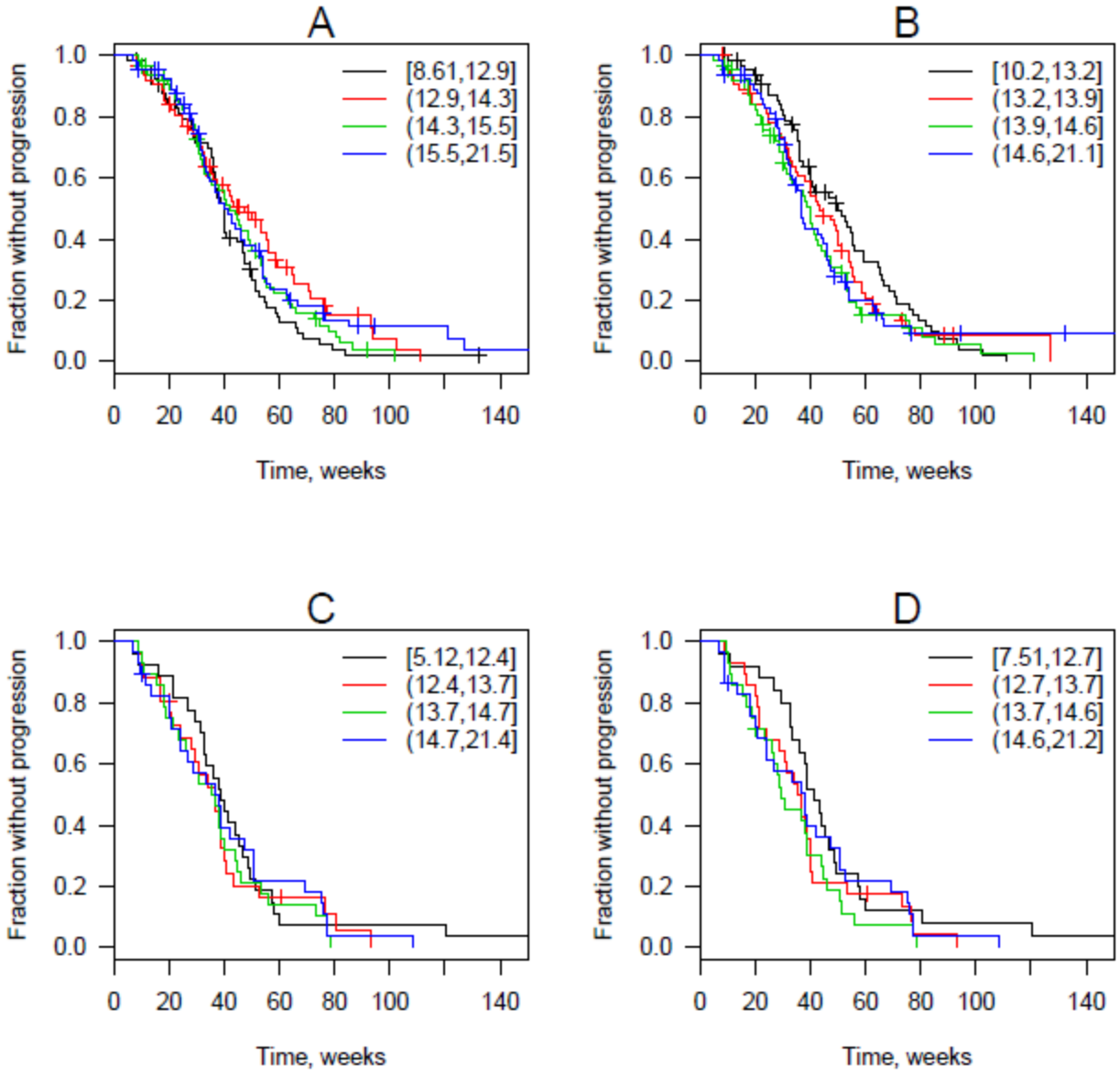
Kaplan Meier plots are shown for patients treated with CAPEOXBEV using raw (A) or mean-normalized (B) expression and patients treated with CAPEOX alone using raw (C) and mean-normalized (D) expression. Hazard ratios (HR) are unadjusted and confidence intervals (CI) are calculated using bootstrapping. The expression intervals shown in the upper right-hand corner are 40-C_t, so higher values correspond to higher expression. Black line = lowest quartile; red line = second quartile; green line = third quartile; blue line = highest quartile.



		Raw expression		Mean-normalized expression	
Cohort	**Quartile**	**HR**	**95% CI**	**HR**	**95% CI**
CAPEOXBEV	1	1	[reference]	1	[reference]
	2	0.67	0.46 – 1.01	0.81	0.57 – 1.30
	3	0.61	0.42 – 0.98	0.68	0.46 – 1.02
	4	0.50	0.34 – 0.78	0.67	0.47 – 1.00
CAPEOX	1	1	[reference]	1	[reference]
	2	0.69	0.39 – 1.19	0.71	0.42 – 1.19
	3	0.61	0.33 – 1.04	0.52	0.30 – 1.05
	4	0.91	0.49 – 1.52	0.99	0.57 – 1.57

Figure S3. Time to disease progression according to quartiles of mir-455-5p expression

Kaplan Meier plots are shown for patients treated with CAPEOXBEV using raw (A) or mean-normalized (B) expression and patients treated with CAPEOX alone using raw (C) and mean-normalized (D) expression. Hazard ratios (HR) are unadjusted and confidence intervals (CI) are calculated using bootstrapping. The expression intervals shown in the upper right-hand corner are 40-C_t, so higher values correspond to higher expression. Black line = lowest quartile; red line = second quartile; green line = third quartile; blue line = highest quartile.

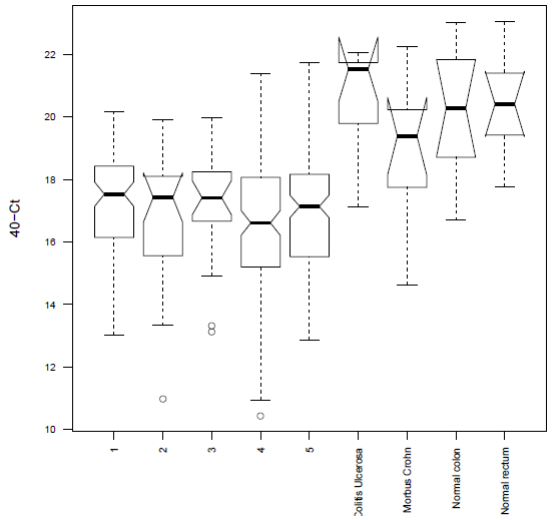


		Raw expression		Mean-normalized expression	
Cohort	**Quartile**	**HR**	**95% CI**	**HR**	**95% CI**
CAPEOXBEV	1	1	[reference]	1	[reference]
	2	0.72	0.50 – 1.03	1.13	0.80 – 1.58
	3	0.88	0.64 – 1.22	1.38	0.99 – 1.91
	4	0.76	0.51 – 1.12	1.25	0.81 – 1.83
CAPEOX	1	1	[reference]	1	[reference]
	2	1.11	0.62 – 2.03	1.27	0.74 – 2.21
	3	1.19	0.74 – 1.98	1.48	0.88 – 2.63
	4	1.03	0.66 – 1.87	1.17	0.67 – 2.02

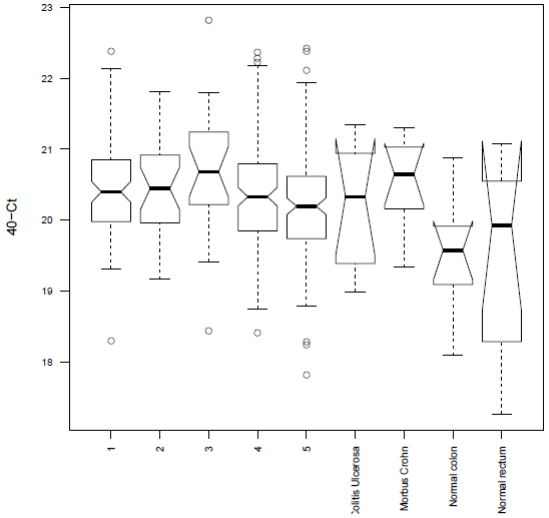
Figure S4. MiRNA expression level in cancer, inflammatory bowel disease and in normal bowel

Group	Number of samples
1 = cecum and ascending colon	87
2 = right flexure and transverse colon	26
3 = left flexure and descending colon	22
4 = sigmoid- and rectosigmoid colon	131
5 = rectum	137
Colitis ulcerosa	10
Crohn's disease	10
Normal colon	10
Normal rectum	10

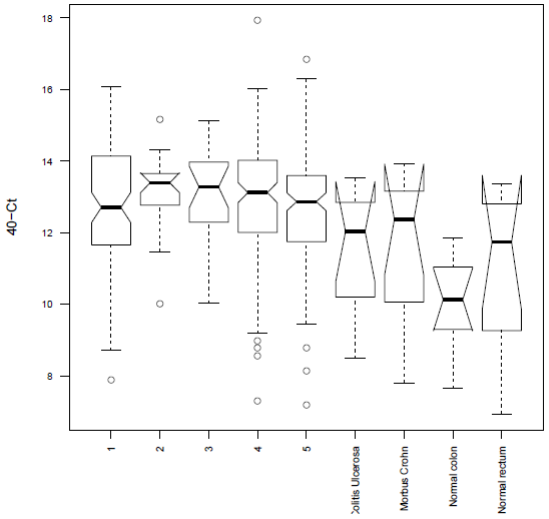
miR-1



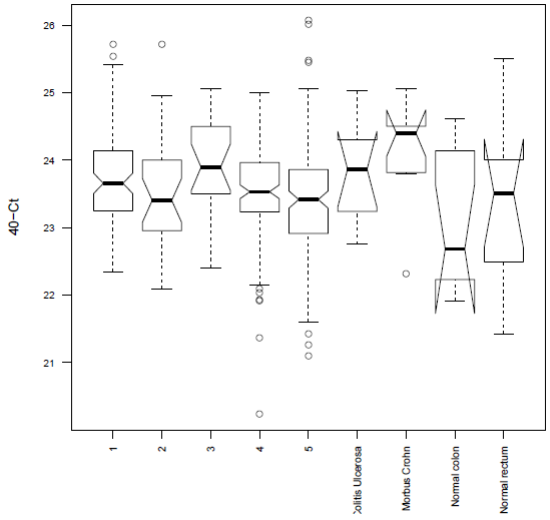
miR-15a-5p



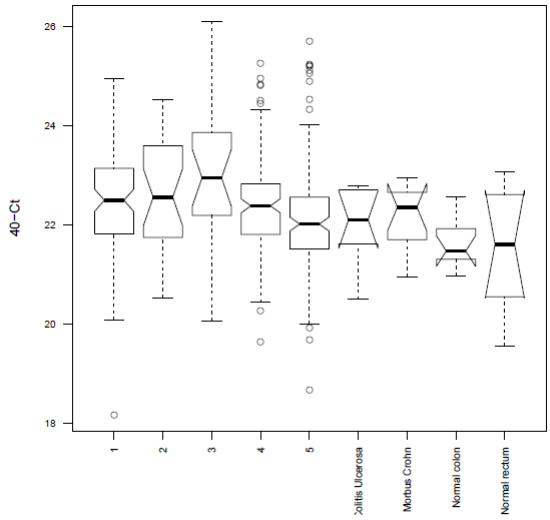
miR-17-3p



miR-22-3p



miR-29b-3p



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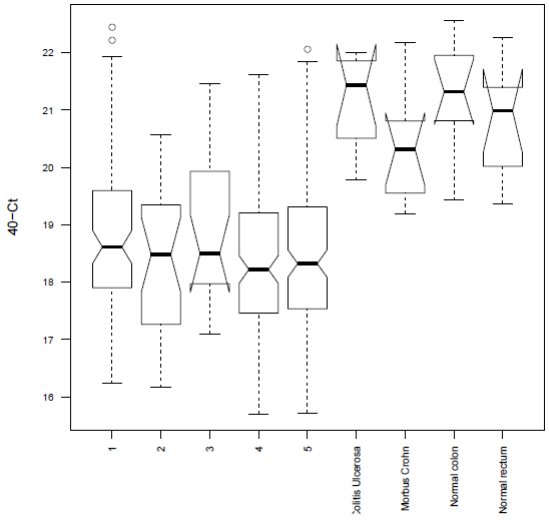
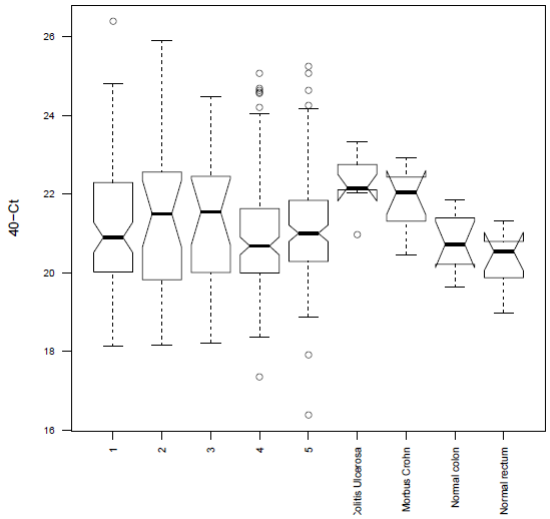


miR-155-5p



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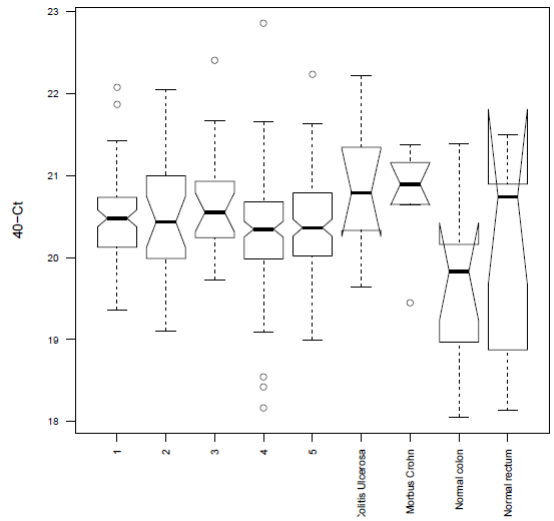
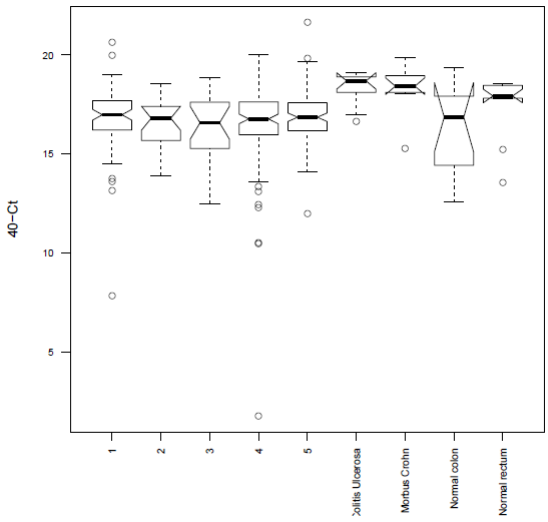
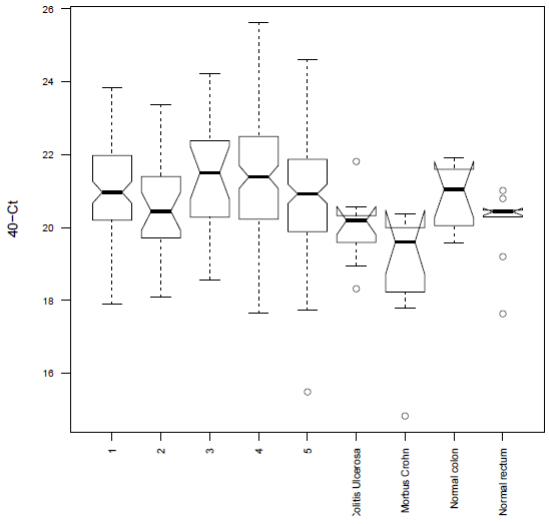


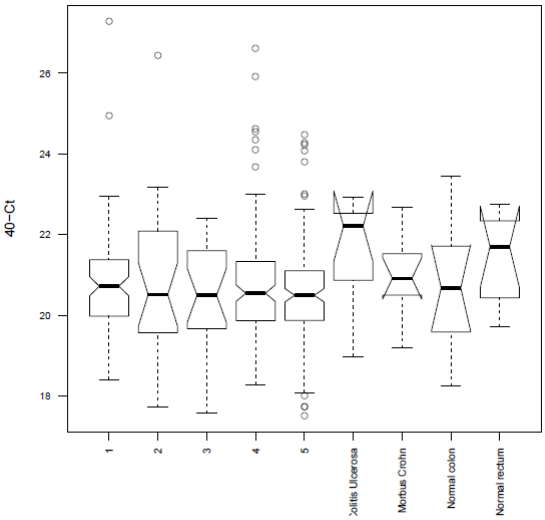
miR-193b-5p



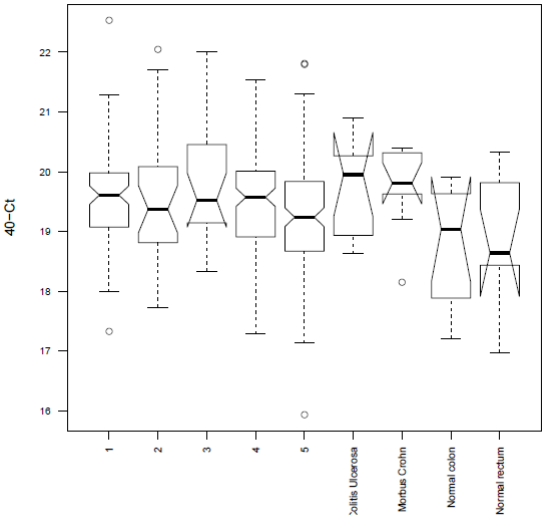
miR-196-5p



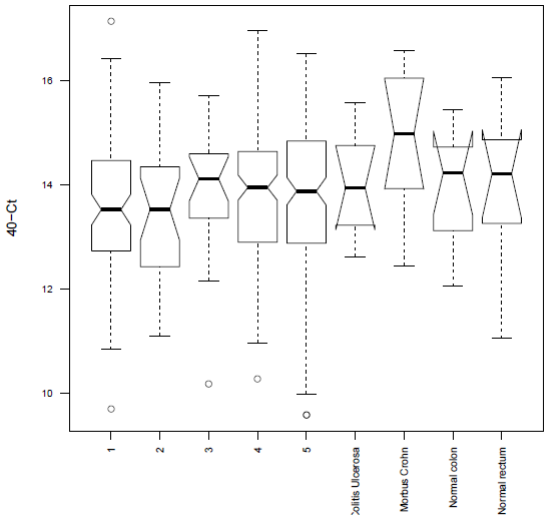
miR-204-5p



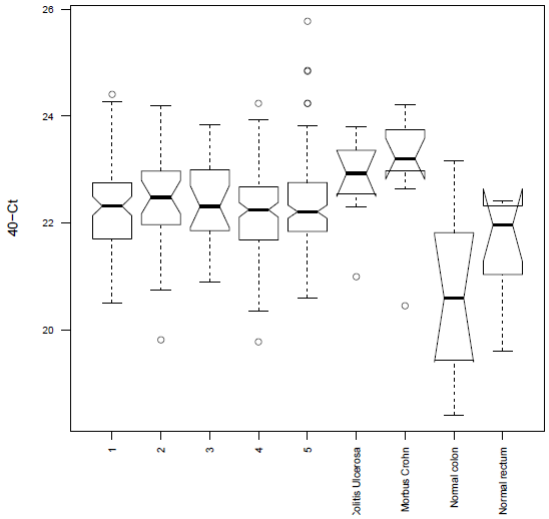
miR-214-5p



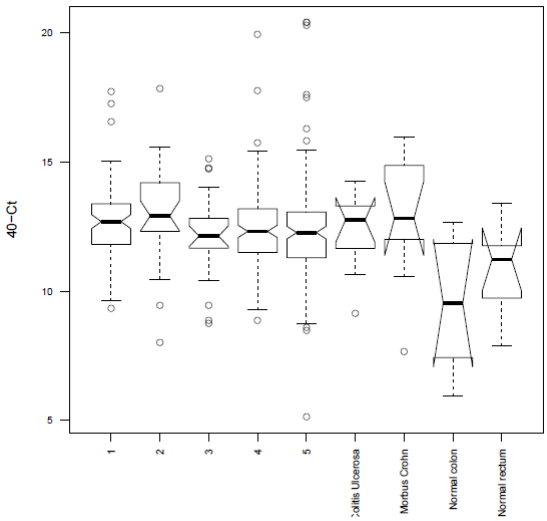
miR-338-3p



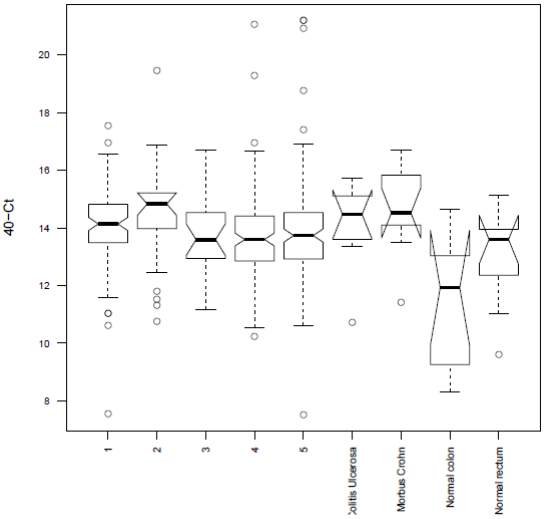
miR-382-5p



miR-449a



miR-455-5p



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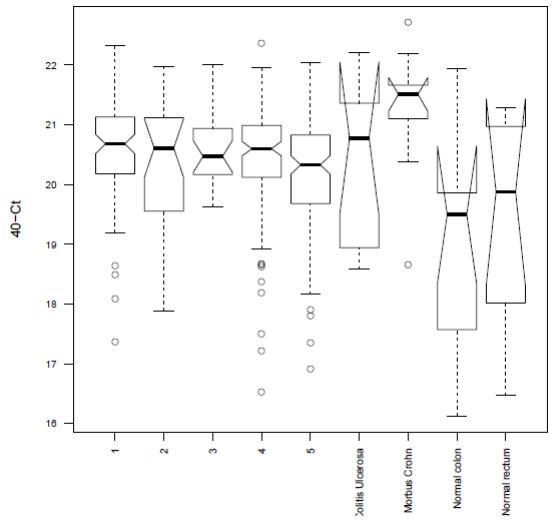
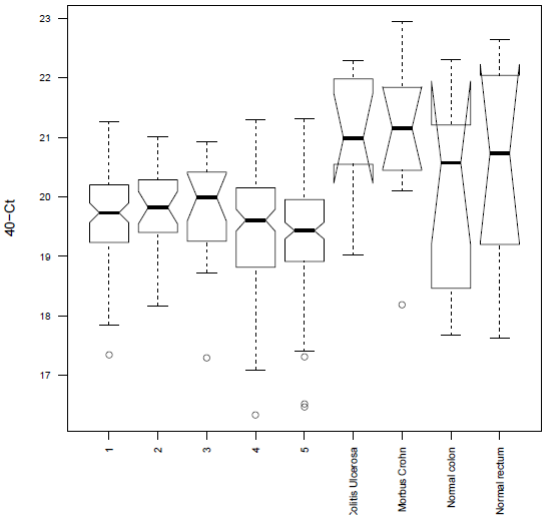


miR-501-5p



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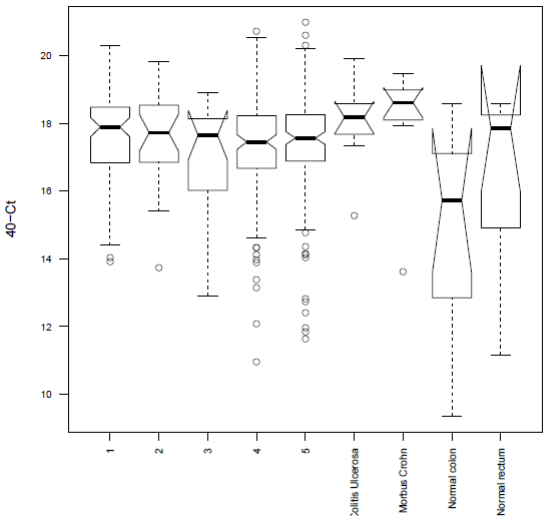
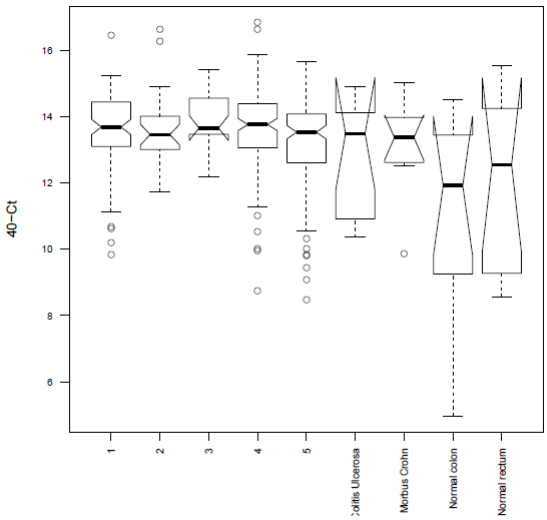
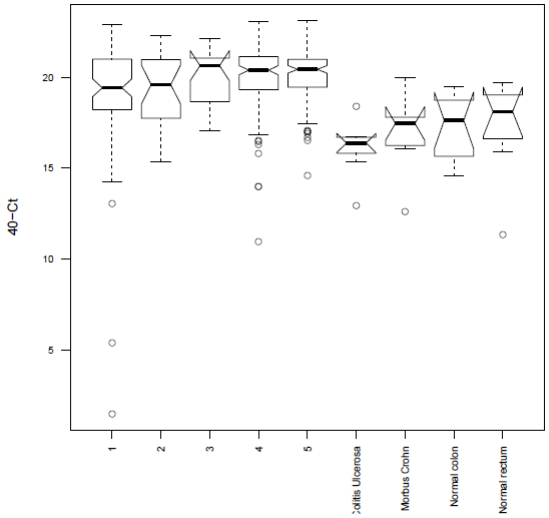


miR-552-3p



miR-592



miR-664-3p

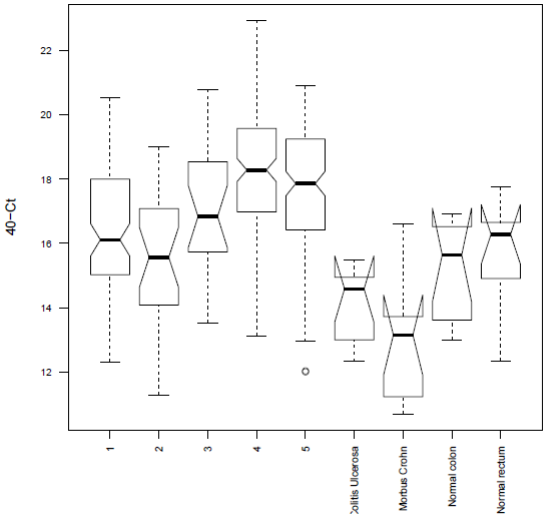
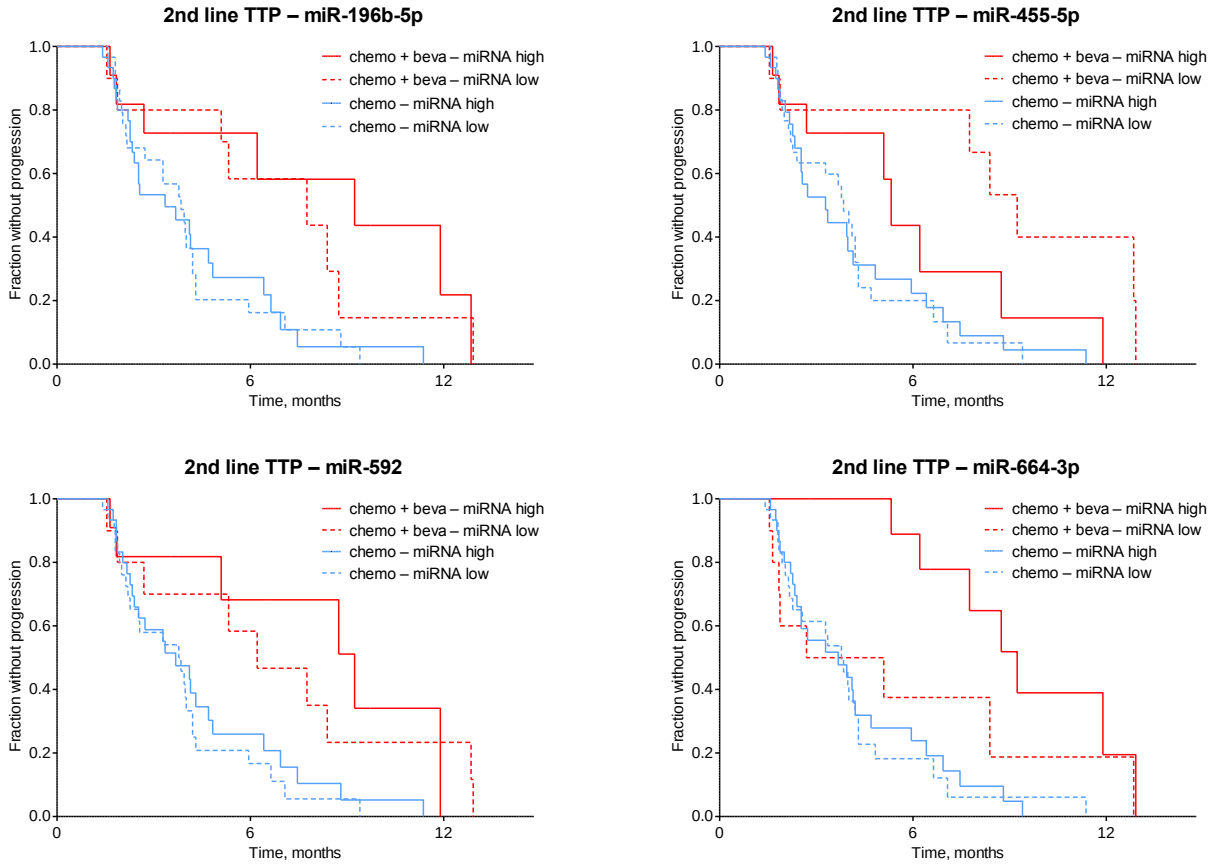


Figure S5. Second line irinotecan-containing regimen time to disease progression (TTP): association with miRNA expression

Kaplan-Meier survival plots

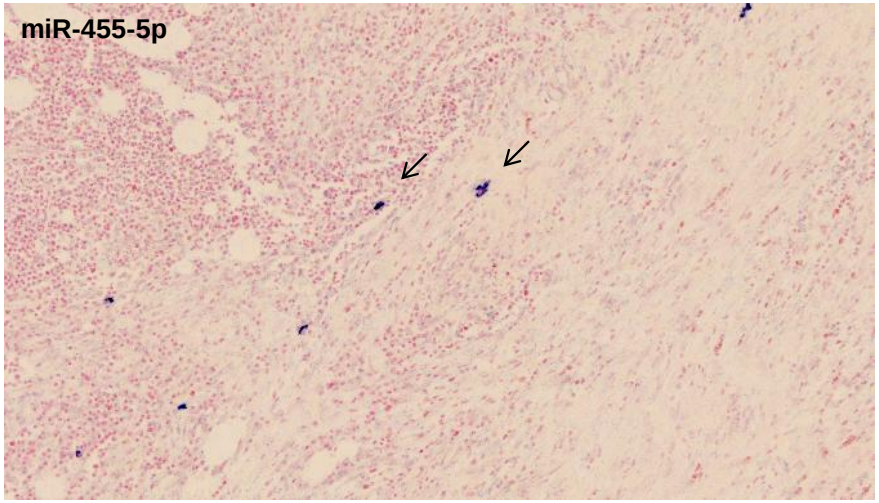


	Chemotherapy alone (n=60)				Chemotherapy + bevacizumab (n=21)			
	Median TTP (months)				Median TTP (months)			
miRNA	**miRNA high (n=30)**	**miRNA low (n=30)**	**HR**	***P*[a]**	**miRNA high (n=11)**	**miRNA low (n=10)**	**HR**	***P*[a]**
miR-196b-5p	3.4	3.8	0.95	0.85	9.2	7.8	0.82	0.71
miR-455-5p	3.3	3.8	0.99	0.98	5.3	9.2	2.72	0.09
miR-592	3.7	3.8	0.80	0.45	9.2	6.2	0.80	0.69
miR-664-3p	3.7	3.8	0.97	0.90	9.2	3.9	0.30	**0.04**

Abbreviations: HR, hazard ratio

[a] log rank test

Figure S6. MiR-455-5p *in situ* hybridization (ISH)



Example of miR-455-5p ISH in a colon cancer specimen. Consecutive sections were stained with LNA probes against miR-455-5p and a scramble sequence. miR-455-5p ISH signal is restricted to a few lymphocyte-like cells (examples indicated by arrows), whereas no ISH signal is obtained with the scramble probe.

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