

SUPPLEMENTARY MATERIAL

Informing metastatic colorectal cancer patients by quantifying multiple scenarios for survival time based on real-life data

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Supplementary Table 1. (1) Median relative survival in months (95% CI) per treatment strategy, and (2) 5-year relative survival of stage IV CRC patients diagnosed between 2008 and 2016.

	Treatment strategy	Year of diagnosis								
		2008	2009	2010	2011	2012	2013	2014	2015	2016
Median relative survival in months	Total stage IV population ^a	11.6 (10.8-12.5)	11.6 (11.0-12.5)	12.2 (11.2-13.1)	12.8 (12.1-13.9)	12.0 (11.3-12.9)	13.2 (12.6-14.0)	14.5 (13.8-15.2)	14.5 (13.4-15.6)	13.2 (12.6-14.3)
	No antitumor treatment ^b	1.6 (1.4-1.8)	1.9 (1.7-2.1)	1.7 (1.4-1.9)	1.8 (1.5-2.0)	1.8 (1.6-2.1)	1.6 (1.4-1.9)	1.7 (1.5-2.1)	1.9 (1.7-2.2)	1.9 (1.7-2.1)
	Any antitumour therapy ^c	16.6 (15.7-17.7)	16.5 (15.5-17.5)	17.9 (16.8-18.8)	18.0 (17.1-19.0)	17.9 (16.6-18.9)	18.6 (17.7-19.5)	19.5 (18.1-20.7)	19.9 (19.0-20.6)	18.8 (17.6-19.8)
	Systemic therapy +/- PTR ^d	16.0 (15.2-17.1)	15.0 (14.1-16.2)	15.9 (14.8-17.1)	15.1 (14.1-16.0)	14.2 (13.4-15.0)	14.9 (14.1-15.9)	15.8 (14.8-16.8)	15.8 (14.5-16.6)	13.9 (13.2-14.8)
	Systemic therapy only ^e	12.4 (11.5-13.6)	12.0 (11.0-13.1)	12.9 (11.9-13.7)	11.7 (10.9-12.4)	11.6 (10.8-12.3)	12.0 (11.0-13.1)	13.7 (12.7-14.6)	12.8 (11.5-13.8)	12.3 (11.1-13.1)
	Systemic therapy + PTR ^f	21.9 (19.8-23.6)	21.4 (19.4-23.8)	20.5 (18.8-22.4)	20.3 (19.1-22.2)	19.3 (17.6-21.1)	20.2 (18.7-22.5)	21.6 (20.0-23.6)	20.3 (19.1-21.8)	19.7 (16.5-24.0)
	Metastasectomy/HIPEC + systemic therapy ^g	57.1 (52.0-84.1)	51.8 (40.6-74.9)	53.6 (47.0-67.1)	57.5 (53.3-75.6)	61.2 (48.4-75.5)	54.3 (48.6-69.8)	*	*	*
	Metastasectomy/HIPEC only ^h	32.9 (25.5-56.7)	52.5 (34.5-91.7)	*	*	*	*	*	*	*
Percentage 5-year relative survival Total stage IV population	11.2 (9.6-13.0)	10.8 (9.6-12.2)	11.8 (10.6-13.2)	13.4 (12.1-14.8)	12.2 (11.0-13.6)	12.3 (11.0-13.6)	15.2 (13.7-16.9)	*	*	

*Results not yet available because of limited follow-up time.

For explanation on the meaning of a,b,c,d,e,f,g,h see the caption of figure 2.

PTR: primary tumour resection. HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Supplementary Table 2. (1) Median **age-standardized** relative survival in months (95% CI) per treatment strategy, and (2) 5-year relative survival of stage IV CRC patients diagnosed between 2008 and 2016.

	Treatment strategy	Year of diagnosis								
		2008	2009	2010	2011	2012	2013	2014	2015	2016
Median age-standardized relative survival in months	Total stage IV population ^a	13.2 (11.4-15.5)	13.1 (11.4-15.5)	14.1 (12.4-16.8)	14.6 (12.6-17.1)	14.0 (11.9-16.5)	14.3 (12.7-16.8)	15.8 (14.1-18.0)	16.0 (13.6-18.4)	14.5 (12.6-16.6)
	No antitumor treatment ^b	1.4 (1.0-2.3)	1.9 (1.3-2.8)	1.3 (1.3-2.5)	1.3 (0.9-2.9)	1.8 (1.3-2.8)	1.6 (1.0-3.1)	1.4 (0.9-3.3)	2.0 (1.2-3.3)	1.5 (1.0-3.0)
	Any antitumour therapy ^c	17.0 (14.9-19.3)	17.0 (14.7-19.9)	18.3 (15.7-20.9)	18.4 (16.1-21.0)	18.4 (16.1-20.4)	18.6 (16.2-21.3)	19.9 (17.2-22.4)	20.1 (18.0-22.7)	18.8 (16.3-21.4)
	Systemic therapy +/- PTR ^d	15.6 (13.4-18.1)	15.1 (12.8-17.5)	15.7 (13.7-18.6)	14.6 (12.7-16.8)	14.3 (12.6-17.6)	14.3 (12.7-17.5)	15.9 (14.1-18.0)	15.6 (13.0-17.9)	14.2 (12.5-16.3)
	Systemic therapy only ^e	11.5 (9.0-15.1)	12.0 (9.8-15.0)	12.8 (10.4-15.6)	11.2 (9.8-13.4)	11.9 (10.3-14.4)	12.0 (10.3-14.9)	14.2 (11.8-16.5)	12.8 (10.3-15.9)	12.5 (10.2-14.7)
	Systemic therapy + PTR ^f	21.5 (17.2-26.2)	21.6 (17.4-28.1)	20.6 (17.4-27.3)	20.3 (17.7-26.1)	19.2 (16.0-26.2)	19.1 (15.0-26.5)	20.4 (15.5-26.1)	20.4 (16.6-28.0)	21.3 (11.2-33.0)
	Metastasectomy/HIPEC + systemic therapy ^g	*	*	*	*	*	*	*	*	*
	Metastasectomy/HIPEC only ^h	*	*	*	*	*	*	*	*	*
Percentage 5-year relative survival Total stage IV population	12.3 (9.0-16.8)	12.5 (9.6-16.4)	13.8 (10.8-17.7)	14.5 (11.4-18.4)	14.0 (10.8-18.0)	13.7 (10.7-17.5)	16.0 (12.6-20.3)	*	*	

*Results not yet available because of limited follow-up time.

For explanation on the meaning of a,b,c,d,e,f,g,h see the caption of figure 2.

PTR: primary tumour resection. HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Supplementary Table 3. Median OS in months (95% CI) and 5-year OS (95% CI) of stage IV CRC patients diagnosed between 2008 and 2016 – stratified by age at diagnosis.

	Age at diagnosis (years)	Year of diagnosis								
		2008	2009	2010	2011	2012	2013	2014	2015	2016
Median OS in months	0-49	18.9 (16.5-22.4)	19.0 (15.5-24.4)	21.1 (15.9-28.6)	19.1 (16.8-23.3)	19.7 (17.4-24.0)	21.8 (17.4-25.1)	22.0 (17.7-25.1)	21.7 (18.2-25.1)	17.4 (15.4-20.7)
	50-59	15.7 (13.8-18.4)	19.4 (16.6-21.2)	19.8 (17.7-21.7)	18.5 (16.6-20.7)	17.8 (14.6-19.8)	17.4 (14.9-19.3)	19.2 (16.6-21.4)	18.4 (16.3-20.9)	18.5 (16.2-20.9)
	60-69	14.8 (13.3-16.2)	13.4 (12.0-15.2)	14.2 (13.2-16.4)	15.2 (13.7-17.1)	14.5 (12.9-15.8)	17.1 (15.1-18.5)	17.0 (15.3-18.8)	19.1 (17.4-20.4)	15.7 (14.3-17.6)
	70-79	8.5 (7.6-10.0)	9.0 (7.9-10.3)	9.9 (8.8-11.0)	10.7 (9.6-11.9)	11.0 (9.7-12.0)	11.1 (9.9-12.5)	12.0 (10.8-13.2)	10.9 (9.6-12.3)	11.6 (9.9-12.8)
	80+	4.0 (3.4-4.6)	4.3 (3.7-5.1)	4.0 (3.5-4.9)	5.1 (4.1-5.9)	4.9 (4.2-5.8)	4.4 (3.8-5.6)	5.8 (5.2-6.8)	5.2 (4.1-6.0)	4.5 (3.9-5.2)
Percentage 5-year OS	0-49	20.5 (15.4-27.3)	22.1 (16.9-28.9)	26.6 (20.8-33.9)	19.3 (14.4-25.8)	19.9 (14.9-26.5)	19.8 (14.9-26.3)	18.4 (13.4-25.2)	*	*
	50-59	11.2 (8.5-14.8)	14.2 (11.3-17.7)	12.6 (9.8-16.1)	14.3 (11.4-17.9)	16.9 (13.6-21.0)	15.1 (12.3-18.7)	18.0 (14.6-22.3)	*	*
	60-69	11.6 (9.6-14.0)	11.2 (9.2-13.6)	11.1 (9.2-13.3)	13.0 (11.0-15.4)	12.9 (11.0-15.2)	13.7 (11.7-16.0)	16.3 (13.9-18.9)	*	*
	70-79	7.4 (4.8-9.3)	6.3 (4.8-8.2)	8.4 (6.8-10.4)	10.1 (8.3-12.2)	7.2 (5.7-9.1)	7.2 (5.7-9.1)	9.5 (7.7-11.7)	*	*
	80+	2.8 (1.7-4.6)	1.7 (0.9-3.2)	2.7 (1.7-4.4)	3.2 (2.1-5.0)	3.1 (1.9-4.8)	2.2 (1.3-3.8)	3.9 (2.6-6.1)	*	*

*Results not yet available because of limited follow-up time.
OS: overall survival. CRC: colorectal cancer.

Supplementary Table 4. Summary table of median OS as reported in mCRC patients participating in clinical trials on first-line systemic therapy.

	Hurwitz 2004	CRYSTAL (Van Cutsem 2009)	FIRE-3 (Heinemann 2014)	TRIBE (Cremolini 2015)	CALGB (Venook 2017)
Treatment arms	IFL-bevacizumab vs. IFL+placebo	FOLFIRI+cetuximab vs. FOLFIRI	FOLFIRI+cetuximab vs. FOLFIRI+bevacizumab	FOLFOXIRI-B vs. FOLFIRI-B	mFOLFOX6/FOLFIRI plus: cetuximab vs. bevacizumab
Inclusion period	2000-2002	2004-2005	2007-2012	2008-2011	2005-2012
Median OS in months	20.3 vs. 15.6	19.9 vs. 18.6	28.7 vs. 25.0	29.8 vs. 25.8	30.0 vs. 29.0
Age of study population					
Mean	59.5 vs. 59.2	-	-	-	-
Median (IQR)	-	61 (range 22-82) vs. 61 (range 19-84)	64.0 (range 38.0-79.0) vs. 65.0 (range 27.0-76.0)	60.5 (52.0-67.5) vs. 60.0 (53.0-67.0)	59.2 (range 20.8-89.5) vs. 59.0 (range 21.8-85.0)
WHO PS (%)					
0	58 vs. 55	55.1 vs. 53.1	52 vs. 54	90 vs. 89	57.6 vs. 58.0
1	41 vs. 44	41.1 vs. 43.4	46 vs. 45	-	42.4 vs. 41.7
2	<1 vs. <1	3.5 vs. 3.5	2 vs. 1	-	0 vs. 0.4
1-2	-	-	-	10 vs. 11	-
Primary tumour site (%)					
- Colon	77 vs. 81	59.8 vs. 60.4	57 vs. 60	-	-
- Rectal	23 vs. 19	38.1 vs. 37.6	39 vs. 36	-	-
- Left colon or rectum	-	-	-	60 vs. 70	61.4 vs. 57.9
- Right colon	-	-	-	35 vs. 24	23.9 vs. 25.4
- Transverse colon	-	-	-	-	5.4 vs. 5.5
- Unknown	-	2.2 vs. 2.0	2 vs. 0	5 vs. 6	9.2 vs. 9.3
Molecular pathology	X	X			
RASwt			58%	19% vs. 9%	100%
RAS mutation			11%	50% vs. 23%	-
BRAF mutation			-	6% vs. 5%	-
Number of metastatic sites* (%)					
1	37 vs. 39	-	40 vs. 42	-	-
>1	63 vs. 61	-	-	-	-
1-2	-	83.5 vs. 86.1	-	-	-
≥2	-	-	59 vs 58	-	-
Liver only	-	20.4 vs. 22.4	31 vs 32	-	32.3 vs. 29.5

*at randomization.

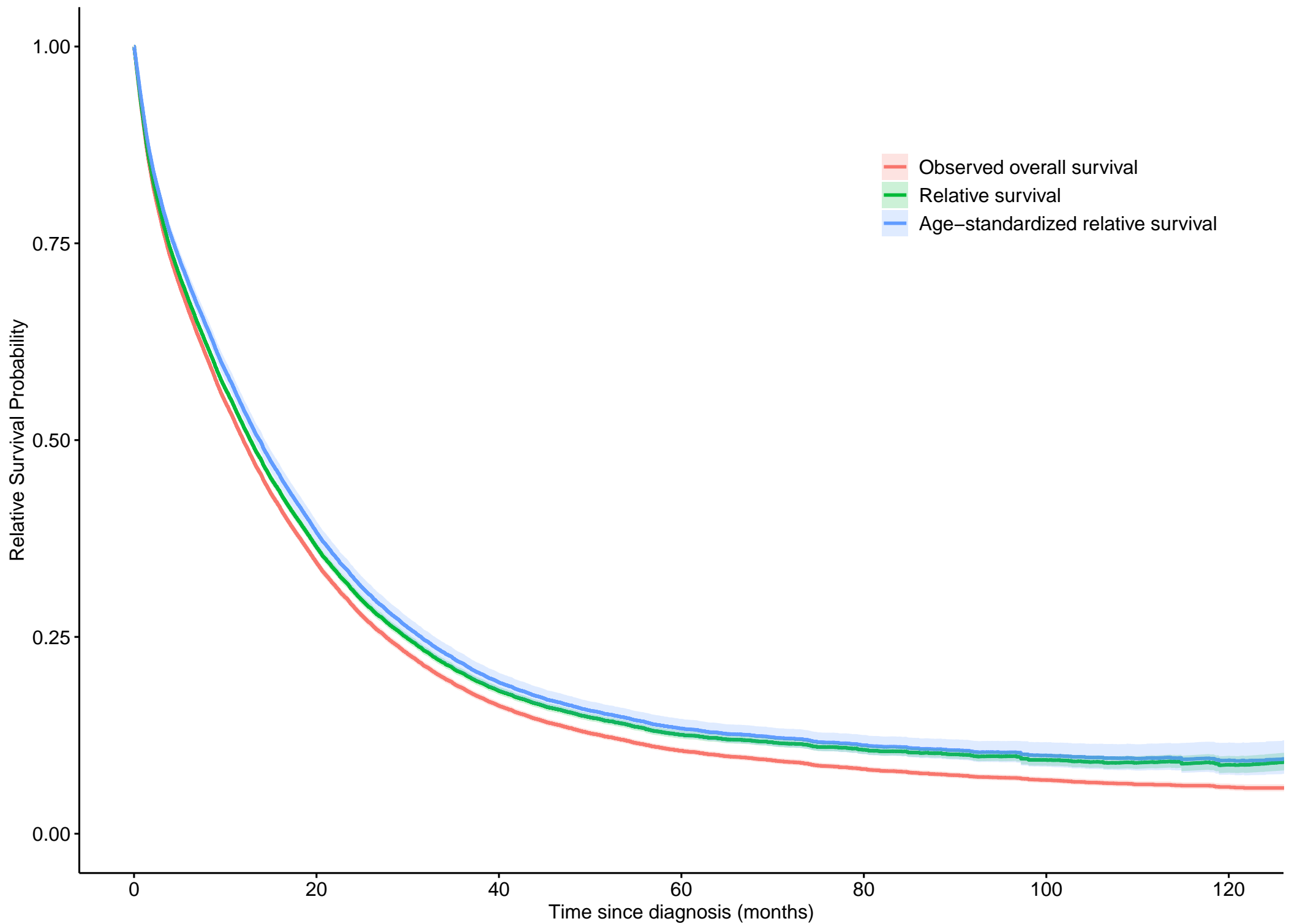
OS: overall survival. PS: performance status. mCRC: metastatic colorectal cancer. IQR: interquartile range.

Multiple scenarios for survival of real-life mCRC patients

	TRIBE2 (Cremolini 2020)
Treatment arms	FOLFOXIRI-B upfront and after progression vs. mFOLFOX6-B followed by FOLFIRI-B
Inclusion period	2015-2017
Median OS in months	27.4 vs. 22.5
Age of study population	
Mean	-
Median (IQR)	60 (53-67) vs. 61 (52-67)
WHO PS (%)	
0	86 vs. 85
1	-
2	-
1-2	14 vs. 15
Primary tumour site (%)	
- Colon	-
- Rectal	-
- Left colon or rectum	62 vs. 62
- Right colon	38 vs. 38
- Transverse colon	-
- Unknown	-
Molecular pathology (%)	
RAS and BRAF wildtype	22 vs. 21
RAS mutation	63 vs. 65
BRAF mutation	10 vs. 10
Missing	5 vs. 5
Number of metastatic sites* (%)	
1	45 vs. 37
>1	55 vs. 63
1-2	-
≥2	-
Liver only	31 vs. 28

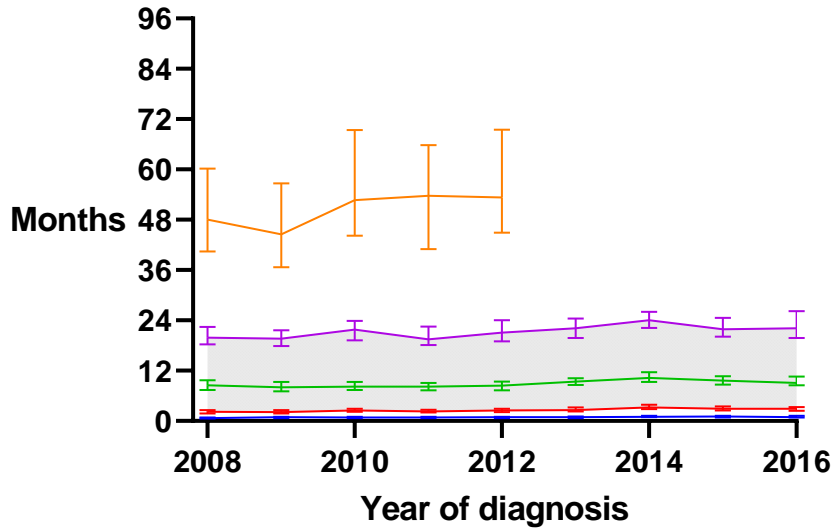
IQR: interquartile range.

Supplementary Figure 1. Kaplan–Meier estimates of Observed overall survival, Relative survival, and Age–standardized relative survival.

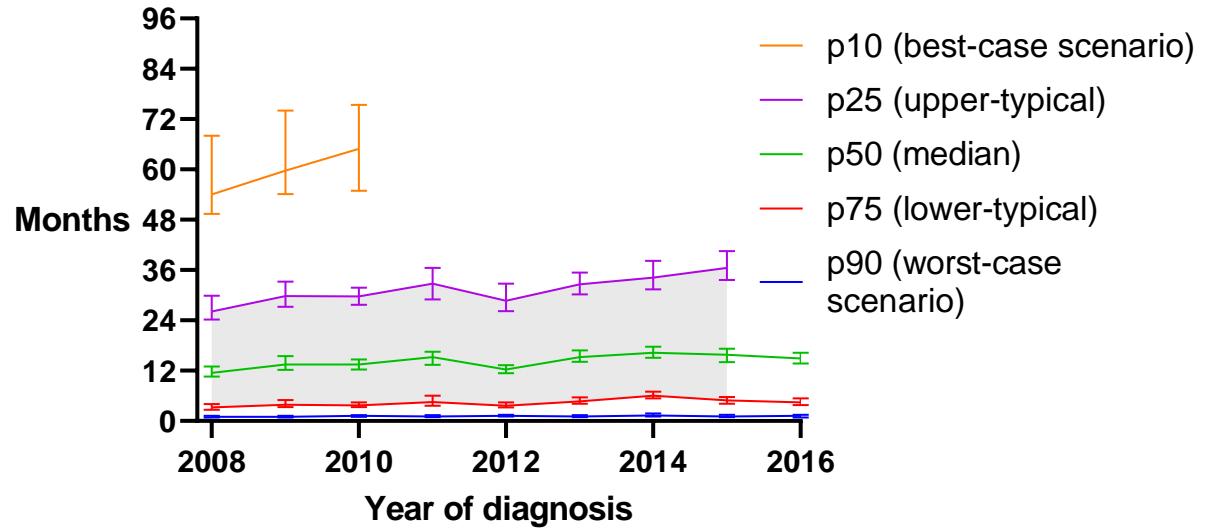


Supplementary Figure 2.
 Change in OS of stage IV CRC patients over time for different scenarios stratified by primary tumour location

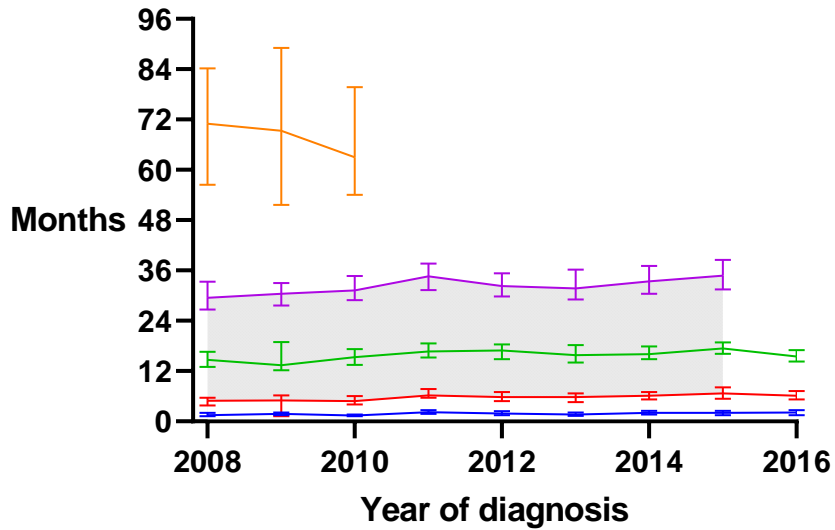
Right-sided colon



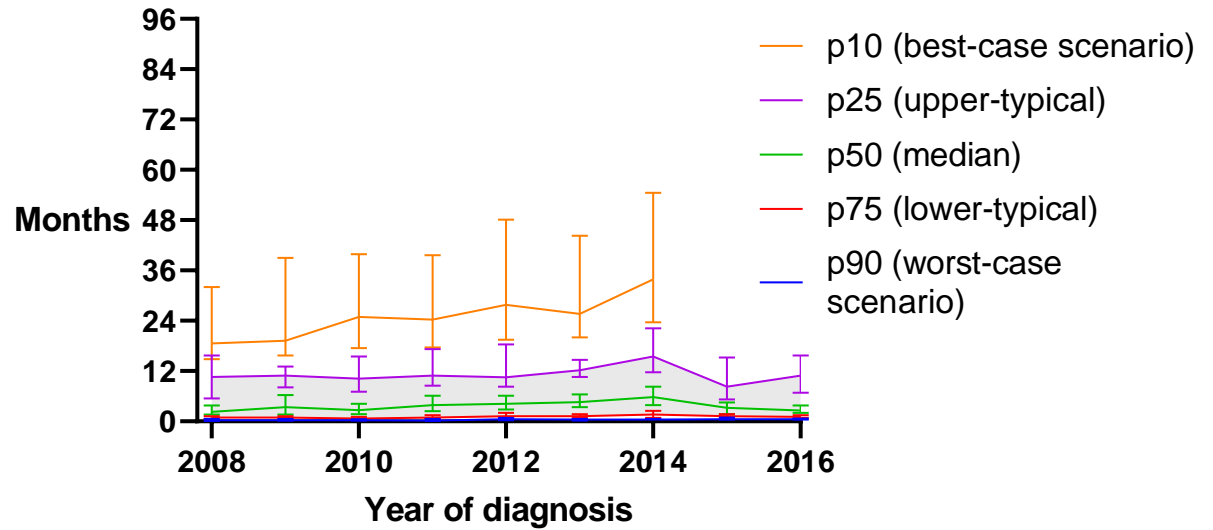
Left-sided colon



Rectum



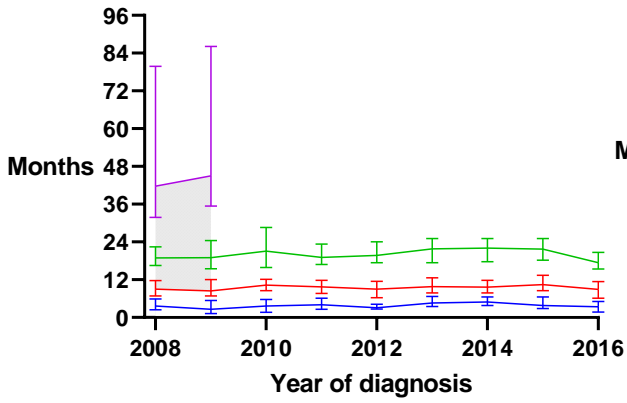
Location primary tumour unknown



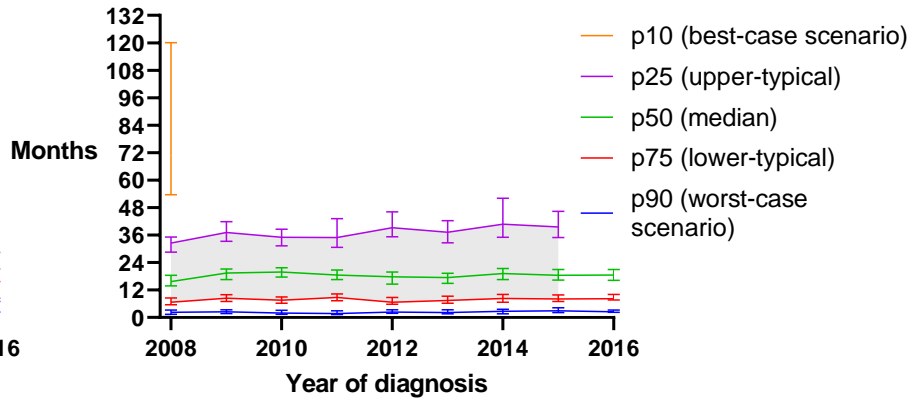
Supplementary Figure 3.

Change in OS of stage IV CRC patients over time for different scenarios stratified by age at diagnosis

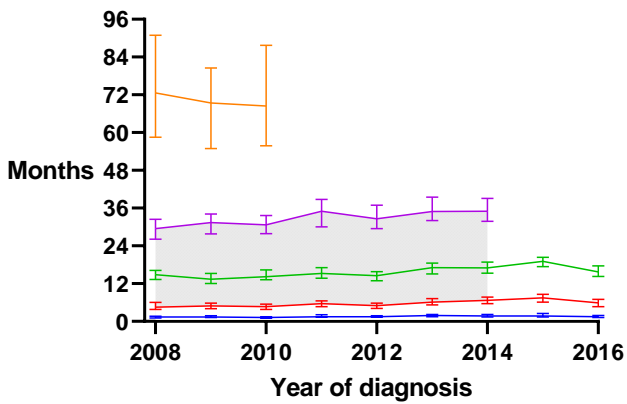
Age 0-49



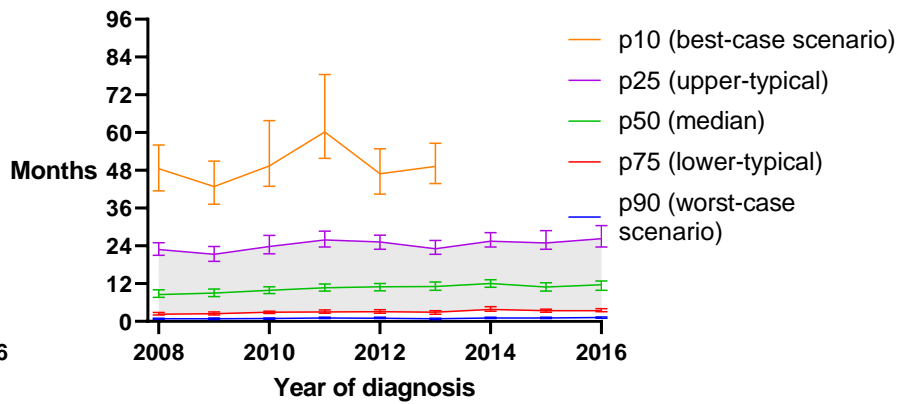
Age 50-59



Age 60-69



Age 70-79



Age 80+

