APPENDIX

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Appendix Table 1. Systemic mini-review of literature for resectability, resection and conversion rates, and outcomes of resections for liver metastases in selected and unselected populations.

Reference	Kanas et al. Clin Epidemiol 2012	Robertson et al. Cancer 2009	Folprecht et al. Ann Oncol 2005		Sjovall et al. Eur J Surg Oncol 2004	Noren et al Eur J Cancer 2016	Scherman et al. BJS Open 2020	Angelsen et al. Br J Surg 2017	Booth et al. Eur J Surg Oncol 2016	Scheele et al. Br J Surg 1990	Hackl et al. BMC Cancer 2014
Population	Meta-analysis	Population	Systemic review	Review	Population	Population	Population	Population	Population	Real life	Population
Unselected vs Selected population	Selected	Selected	Selected	Unselected	Unselected	Unselected	Unselected	Unselected	Unselected	Unselected/ selected	Unselected
Single-site vs multisite metastases	Single-site	Single-site	Single-site	Multi-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site
Prospective vs retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Study name/definition	**Review**	**USA**	**Review**	**Review**	**Swedish**	**Swedish**	**Swedish**	**Norwegian**	**Canadian**	**German**	**German**
Treatment arm or study population	**86studies**	**Medicare (1 site)**	**5studies**	**14 studies**	**Population (1 region)**	**Population based**	**Population based (nationwide)**	**Population based**	**Canadian (1 region)**	**Not resectable vs resectable not resected vs resected**	**Population-based (30 centres)**
Inclusion period	**<2010**	**2000-2004**	**<2005**	**<2005**	**1996-1999**	**2007-2011**	**2009-2013**	**2011-2013**	**1994-2009 (1994-1999→ 2005-2009)**	**1960-1987**	**2002-2007**
Number of patients	20,745	3957	503	3349	508	3149	1325	2960	2717	1209	1426
Target population	Liver metastases	Liver metastases	Liver metastases	mCRC	Liver metastases	Synchronous liver metastases	Liver metastases	Liver metastases	Liver metastases	Liver metastases	Liver metastases
Age, median (range)					73 (30-95)		66 (25-87)	71 (23-104)	64 (14-94)	60 (22-91)	68
Elderly (>70 years if not noted otherwise)		73 %				31% (>75)			16% (>75)		42 %
Male gender		55 %			50 %	59 %	61 %	56 %	59 %	61 %	61 %
PS 0											
PS 2-3											
Single-site metastases					52 %	100 %		57 %			
Median number metastatic sites					1	1		1			
Synchronous metastases					64 %	100 %	56 %	24 %		59 %	71 %
Liver metastases					100 %	100 %	100 %	100 %	100 %	100 %	100 %
Liver only					52 %	100 %		57 %	majority		
Lung metastases								23 %			
Lung only											
Target site metastases only											
Rectal primary tumour					0 %	30 %	35 %				32 %
Colon primary tumour					100 %	70 %		72 %			68 %
Right colon					55 %	35 %	24 %				
Left colon					45 %	35 %	38 %				
Primary tumour resection											
Prior radiotherapy for primary tumour											
Prior adjuvant therapy for primary tumour											
KRAS / RAS wild-type											
KRAS ± NRAS mutant											
BRAFV600E mutant											
Technical resectability rate					10% (upfront)						
Response rate to systemic therapy	48-73%	31-81%									
Duration of systemic therapy (months)											
Conversion rate											
Resection rate R0-1	24-54%				4% all / 8% liver-only			18 %	2→4% of all mCRC	18 %	26 % (17%→32%)
Resection rate R0-2		Only resected		1-26%		18 %		20 %		19 %	
Local ablative therapy					2% all/5% liver-only						
Mean number of resections/LAT											
Pre-metastasectomy chemotherapy						18 %			11→38%		
Post-metastasectomy adjuvant therapy											
Perioperative therapy									44→65%		
Duration of systemic therapy											
Median OS (months) *	43 (20-88)	27			12 (treatment) - (resected)	9 (not resected) 57 (resected		11 all / >48 resected	36→52	7-14 not /13-25 resectged	52 resected/ 23 not
OS 1/3/5-year rate – resected*	-/30-80/16-74%	75/45/25%			-/53%/-	-/-/45%	90/70/50%	93/73%/-	-/-/36→46%	80/38/31%	-/-/32%
OS 1/3/5-year rate all*					40/12/3%						-/-/18% not resected
Median PFS (months)*											
Median RFS or DFS (months)*			9-33								
RFS or DFS rate 1/3/5-year resected*	-/-/7-48%										

References: Kanas[1], Robertson[2], Folprecht[3], Sjovall[4], Noren[5], Scherman[6], Angelsen[7], Booth[8], Scheele[9], Hackl[10]

* Extrapolation from curve if not presented in text

Appendix Table 2. Systemic mini-review of literature for resectability, resection and conversion rates, and outcomes of resections for lung, lymph node, peritoneal and local recurrence in selected and unselected populations.

Reference	Tampellini et al. Oncologist 2012	Li et al. World J Gastroenterol 2010	Guerrera et al. J Thorac Dis 2016	Booth et al. Ann Surg Oncol 2016	Isom et al. Surg Oncol 2020	Elias et al. J Clin Oncol 2010	Kyang et al. J Surg Oncol 2019	Al-Busaidi et al. ANZ J Surg 2019	Ursem et al. Oncologist 2020	Ikoma et al. J Clin Oncol 2017	Yun et al. Medicine 2016
Population	Population	Real-world	Population	Population	Population	Population	Population	Population	Population	Population	Population
Unselected vs Selected population	Selected	Unselected	Selected	Selected	Selected	Selected	Selected	Selected	Unselected	Unselected	Unselected
Single-site vs multisite metastases	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site	Single-site
Prospective vs retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Study name	**Italian**	**Conversion unresectable**	**Italian**	**Canadian**	**USA**	**French speaking countries**	**Australian**	**New Zealand**	**USA**	**USA**	**South Korea**
Treatment arm or study population	**(3 centres)**	**Real-world (1 center)**	**Population-based (1 institution)**	**Population-based (1 region)**	**Population based (SEER)**	**Population-based (23 centres)**	**Region**	**Population based (1 region)**	**Population-based (single institution)**	**Population-based (single institution)**	**Population-based (single institution)**
Inclusion period	**1994-2010**	**2003-2008**	**2004-2012**	**1994-2009**	**2004-2013**	**1990-2007**	**1996-2018**	**2000-2016**	**2009-2017**	**1993-2008**	**1994-2008**
Number of patients	409	70	188	709 (126,283 CRC)	90 resected/749 n	523	363	31	108	27	147
Target population	Lung metastases	Lung conversion	Lung metastases	Operated lung metastases	Operated lymph nodes	Peritoneal carcinomatosis	Peritoneal carcinomatosis	Ovarian metastases	Ovarian metastases	Local recurrence	Local recurrence
Age, median (range)	63 (27-87)		66 (58-72)	65	63 (54-74)	54 (16-88)		55 (28-77)	50 (19-106)	56 (48-68)	58 (22-87)
Elderly (>70 years if not noted otherwise)		40% (>60)		17% (>75)							45% (>60)
Male gender	59 %	30 %	58 %	52 %	50 %	43 %	44 %	0 %	0 %	44 %	57 %
PS 0	0-1 77%		63 %			76 %					
PS 2-3	5 %		15 %	majority		4 %					
Single-site metastases	38 %		68 %					19 %		100 %	
Median number metastatic sites	1		1							1	
Synchronous metastases	22-43%	27 %				35 %		71 %	64 %	0 %	
Liver metastases	55 %		28 %	30 %		15 %			43 %		
Liver only	0 %		0 %	0 %		0 %					
Lung metastases	100 %	100 %	100 %	100 %					15 %		
Lung only	47 %	100 %									
Target site metastases	89 %				100 %	83 %		other present	12 %	100 %	72 %
Rectal primary tumour	35 %	67 %			41 %	8 %		24 %		100 %	100 %
Colon primary tumour	65 %	33 %			59 %	92 %		76 %		0 %	0 %
Right colon						42 %			25 %		
Left colon						50 %			50 % (left+rectum)		
Primary tumour resection					100 %	100 %		87 %	71 %	100 %	100 %
Prior radiotherapy for primary tumour										100 %	20 %
Prior adjuvant therapy for primary tumour									82 %		
KRAS / RAS wild-type									44% (31% unknown)		
KRAS ± NRAS mutant									26 %		
BRAFV600E mutant									6% (43% unknown)		
Technical resectability rate	8 % (upfront)	6 (0%)							77% (upfront unknown)		
Response rate to systemic therapy	36-74%	36%									
Duration of systemic therapy (months)											
Conversion rate	5 %	6 %									
Resection rate R0-1	12 %		99 % (only resected)			85 % (only resected)		43 %		43 %	
Resection rate R0-2		6 %	1 %	0.3→1% of all CRC	11 %	100 %		94 %	77 %		29% of local only
Local ablative therapy						0 %					
Mean number of resections/LAT						1.04					
Pre-metastasectomy chemotherapy		100%		5→11%		71 %					20%
Post-metastasectomy adjuvant therapy	100 %			20→35%		47 %		68 %			71-90 %
Perioperative therapy	38 %			22→40%							
Duration of systemic therapy											
Median OS (months)*	72 resected/ 24-31 not	19 all		36→51 resected	33 resected/ 29 not	30	35	31 resected/ 24 not	37 resected/ 25 not	43 resected/ 38 not	100 resected/ 20 not
OS 1/3/5-year rate – resected*	98/93/75'%	50% (2 yr)?	95/68/53%	-/-/40%	76/42/30%	81/41/27%	-/49/33%	-/-/30% R0		80/70/40%	100/82/58%
OS 1/3/5-year rate all*	90/30/10%	39% (2 yr)						-/-/12%	-/-/11	80/65/35%	75/37/19%
Median PFS (months)	26 resected/ 10-11 not	8 all									
Median RFS or DFS or TTR (months)*							11	11		8	
RFS or DFS rate 1/3/5-year resected*	95/50/28%		-/-/33%			47/15/10%	-/20/16%				

References: Tampellini[11], Li[12], Guerrera[13], Booth[14], Isom[15], Elias, Kyang[16], Al-Busaidi[17], Ursem[18], Ikoma[19], Yun[20]

* Extrapolation from curve if not presented in text

Appendix Table 3. Systemic mini-review of literature for resectability, resection and conversion rates, and outcomes of resections for multisite metastases in randomized studies.

Reference	Sorbye et al. Ann Oncol 2007	Folprecht et al. Lancet Oncology 2010		Gruenberger et al. Ann Oncol 2015		Cremolini et al. Lancet Oncol 2015		Douillard et al. Eur J Cancer 2015		Venook et al JAMA 2017		Stintzing et al. Lancet Oncol 2016; Heinemann et al Lancet Oncol 2014	
Population	Phase II-III randomized	Phase II randomized		Phase II randomized		Phase III randomized		Phase III randomized		Phase III randomized		Phase III randomized	
Unselected vs Selected population	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected	Selected
Single-site vs multisite metastases	Multisite	Single-site (liver)		Multisite		Multisite		Multisite		Multisite		Multisite	
Prospective vs retrospective	Prospective	Prospective		Prospective		Prospective		Prospective		Prospective		Prospective	
Study name		**CELIM**		**OLIVIA**		**TRIBE**		**PRIME**		**CALGB 80405**		**FIRE-3**	
Treatment arm or study population	**Median per study (Range all studies)**	**FOLFOX + cetux.**	**FOLFIRI + cetux.**	**FOLFOXIRI+ bev.**	**FOLFOX + bev.**	**FOLFIRI + bev.**	**FOLFOXIRI + bev.**	**FOLFOX + panit.**	**FOLFOX**	**Doublet + bev.**	**Doublet + cetux.**	**FOLFIRI + cetux.**	**FOLFIRI + bev.**
Inclusion period	**2001-2005**	**2004-2008**		**2008-2011**		**2008-2011**		**2006-2008**		**2005-2012**		**2007-2012**	
Number of patients	21,214 mCRCs	56	55	41	39	256	252	253	252	559	578	199	201
Target population	Study patients with mCRC	Unresectable liver metastases		mCRC Liver conversion		mCRC		mCRC		KRAS exon 2 wild-type mCRC		KRAS exon 2 wild-type mCRC	
Age, median (range)	62	65 (57-71)	62 (56-68)	63 (32-77)	57 (28-80)	60 (53-67)	61 (52-68)	61 (27-81)	61 (24-82)	59 (22-85)	59 (21-90)	64	65
Elderly (>70 years if not noted otherwise)												32 %	25 %
Male gender	60% (33–81%)	64 %	64 %	71 %	46 %	61 %	60 %	67 %	63 %	62 %	60 %	73 %	66 %
PS 0	52% (8–98%)			56 %	80 %	89 %	90 %	94 % (0-1)	93 % (0-1)	58 %	58 %	54 %	54 %
PS 2-3	6% (0–34%)			5 %	0 %			6 %	7 %	0,4 %	0 %	2 %	1 %
Single-site metastases	52% (5–100%)	100 %	100 %	100 %	100 %			0-19%	0-16%			43 %	41 %
Median number metastatic sites	1	1	1	1	1							2	2
Synchronous metastases	59% (36–81%)			73 %	82 %	81 %	78 %			80 %	77 %		
Liver metastases	76% (25–100%)	100 %	100 %	100 %	100 %			86 %	85 %	74 %	73 %	85 %	82 %
Liver only		100 %	100 %	100 %	100 %	18 %	23 %	19 %	16 %	30 %	32 %	36 %	31 %
Lung metastases	30% (3–62%)							8 %	12 %	33 %	32 %		
Lung only								0 %	0 %				
Lymph node metastases	19% (7–58%)												
Lymph nodes only													
Peritoneal metastases	11% (2–24%)									23 %	23 %		
Peritoneal only													
Ovarian													
Ovarian-only													
Local relapse													
Local relapse-only													
Rectal primary tumour	32% (0-73%)	38 %	51 %					35 %	35 %				
Colon primary tumour	68% (27–100%)	62 %	49 %					65 %	65 %				
Right colon						24 %	35 %			31 %	30 %		
Left colon										60% rectum included	61% rectum included		
Primary tumour resection	89% (50–100%)			39 %	31 %	65 %	69 %			73 %	75 %	86 %	89 %
Prior radiotherapy for primary tumour	14% (0–81%)	2 %	15 %									12 %	13 %
Prior adjuvant therapy for primary		11 %	22 %					17 %	15 %			19 %	19 %
KRAS / RAS wild-type		63 %	64 %			49%	48%			100/86%	100%/84%	100 /- %	100 /- %
RAS+BRAF wild-type								100 %	100 %				
KRAS ± NRAS mutant		27 %	25 %							14 %	16 %		
BRAFV600E mutant		4 %	2 %			6%	8%						
Technical resectability rate		32 %		0 %	0 %							23 %	20 %
Response rate to systemic therapy		68 %	57 %	81 %	62 %	54 %	65 %	60 %	47 %			65 %	59 %
Duration of systemic therapy (months)				8	6			6	6	6	6	7	8
Conversion rate		28 %†		61 %†	49 %†							14 %	12-13 %
Resection rate R0-1		40 %†	38 %†	51 %†	33 %†	12 %	15 %	10 %	8 %	12% total			
Resection rate R0-2		42 %†	44 %†	61 %†	49 %†			14 %	12 %				
Local ablative therapy		9 %†	6 %†										
Mean number of resections/LAT													
Pre-metastasectomy chemotherapy		100 %	100 %	100%	100%								
Post-metastasectomy adjuvant therapy		Intent in 51%	Intent in 49%										
Perioperative therapy		100 %	100 %										
Duration of systemic therapy													
Median OS (months)*				Not reached	32	26	30	26	20	29 (62 resected)	30 (65 resected)	33	25
OS 1/3/5-year rate – resected*													
OS 1/3/5-year rate all*						87/35/13%	85/42/36%			76/38/16%	76/42/21%	88/47/18%	87/33/7%
Median PFS (months)*				19	12	10	12	11	9	11	11	8	10
Median RFS or DFS (months)*				17	8								

References: Sorbye[21], Folprecht[22], Gruenberger[23], Cremolini[24], Douillard[25], Venook[26], Stintzing[27], Heineman et al[28]

† of borderline or >4 metastases

* **Extrapolation from curve if not presented in text**

METHODS – STUDY DESIGN AND PARTICIPANTS: STUDY CENTRES

Appendix Table 4. Presentation of 21 participating hospitals with recruitment per centre, and multidisciplinary team (MDT) assessment principles at local hospitals and centralization principles for organ-specific MDTs in panel A. Investigators from 21 participating hospital in panel B

A.

	Hospital	Recruitment period (months)	Included / eligible	Recruitment%	Preop MDT colon/ rectal	Postop MDT colon/ rectal	Organ specific MDT	Local MDT liver	Local MDT lung	Local MDT peritoneum	Local MDT LAT	Most demanding cases
1	Helsinki university hospital	70	371	49	All	Selected	Selected	Helsinki	Helsinki	Helsinki	Helsinki	Helsinki
2	Tampere university hospital	56	129	40	All	All	Selected	Tampere	Tampere	Helsinki	Tampere	Helsinki
3	Turku university hospital	59	150	56	Selected	All	Selected	Turku	Turku	Helsinki	Turku	Helsinki
4	Oulu university hospital	68	176	73	All	All	Selected	Oulu	Oulu	Oulu	Oulu	Helsinki
5	Kuopio university hospital	40	34	49	All	All	Selected	Kuopio	Kuopio	Helsinki	Kuopio	Helsinki
6	Central Finland Central Hospital	49	89	54	All	All	Selected	Keski-Suomi	Keski-Suomi	Oulu	Tampere/ Helsinki	Helsinki
7	Satakunta central hospital	49	63	70	Colon all, rectal selected	Colon all, rectal selected	Selected	Turku/ Helsinki	Turku/ Helsinki	Helsinki	Turku/ Helsinki	Helsinki
8	Päijät-Häme central hospital	19	11	47	Selected	Selected	Selected	Tampere/ Helsinki	Tampere/ Helsinki	Helsinki	Tampere/ Helsinki	Helsinki
9	South Ostrobothnia central hospital	7	1*	8	Selected	Selected	Selected	Tampere	Tampere	Helsinki	Tampere	Helsinki
10	Kymenlaakso central hospital	7	2*	32	Selected	Selected	Selected	Helsinki	Helsinki	Helsinki	Helsinki	Helsinki
11	Kanta-Häme central hospital	31	30	31	Selected	Selected	Selected	Helsinki	Helsinki	Helsinki	Helsinki	Helsinki
12	North Carelia central hospital	8	6*	22	Selected	Selected	Selected	Keski-Suomi	Kuopio	Oulu	Kuopio	Helsinki
13	Vaasa Central hospital	19	11	40	All	All	Selected	Helsinki	Helsinki	Helsinki	Turku	Helsinki
14	South Carelia central hospital	14	1*	16	Selected	Selected	Selected	Helsinki	Helsinki	Helsinki	Helsinki	Helsinki
15	Lapland central hospital	28	1*	21	Selected	Selected	Selected	Oulu	Oulu	Oulu	Oulu	Helsinki
16	South Savo central hospital	21	3*	31	Selected	Selected	Selected	Keski-Suomi	Keski-Suomi	Oulu	Kuopio	Helsinki
17	Kainuu central hospital	28	1*	23	Very selected	Very selected	Selected	Oulu	Oulu	Oulu	Oulu	Helsinki
18	Central Ostrobothnia central hospital	35	3*	29	Selected	Selected	Selected	Oulu/ Helsinki	Oulu/ Helsinki	Oulu/ Helsinki	Oulu/ Helsinki	Helsinki
19	Länsi-Pohja central hospital	7	1*	24	Selected	Selected	Selected	Oulu	Oulu	Oulu	Oulu	Helsinki
20	East Savo central hospital	7	1*	58	Selected	Selected	Selected	Kuopio	Kuopio	Oulu	Kuopio	Helsinki
21	Åland central hospital	14	2*	61	Selected	Rectal selected, colon no	Selected	Turku	Turku	Helsinki	Turku	Helsinki
		Median 28	Total 1086	Median 40%								

MDT= multidisciplinary team. Preop= preoperative MDT at colon/rectal cancer diagnosis. Postop= postoperative MDT after primary surgery
LAT= local ablative therapy (thermal ablation, SIRT= selective intra-arterial radiotherapy, TACE= transarterial chemoembolizatioon, radiotherapy mostly as SBRT= stereotactic body radiotherapy)
Selected refers to local hospital decision to refer only potentially/borderline resectable patients to MDT assessment.

* No nurse coordinator available, fully oncologist driven.

B.

Hospital	**Investigators**
Helsinki University Hospital	Pia Österlund, Helena Isoniemi, Leena-Maija Soveri, Päivi Halonen, Arno Nordin, Aki Uutela, Heikki Mäkisalo, Riikka Huuhtanen, Eila Lantto, Ali Ovissi, Juhani Kosunen, Sirpa Leppä, Petri Bono, Johanna Mattson, Jari Räsänen, Anna Lepistö, Emerik Österlund, Heidi Penttinen, Siru Mäkelä, Ari Ristimäki, Olli Carpén, Eila Lantto, Nina Lundbom, Antti Hakkarainen, Marjut Timonen.
Tampere University Hospital	Tapio Salminen, Pia Österlund, Kaisa Lehtomäki, Veera Salminen, Niina Paunu, Irina Rinta-Kiikka, Martine Vornanen, Nieminen Lasse
Turku University Hospital	Annika Ålgars, Raija Ristamäki, Eetu Heervä, Johanna Virtanen, Eija Korkeila, Eija Sutinen, Maija Lavonius, Jari Sundström, Roberto Blanco
Oulu University Hospital	Raija Kallio, Markus Mäkinen, Eija Pääkkö
Kuopio University Hospital	Annamarja Lamminmäki, Hanna Stedt, Tiina Tuomisto-Huttunen, Päivi Auvinen, Vesa Kärjä, Sakari Kainulainen, Hannu-Pekka Kettunen
Central Finland Central Hospital	Ilmo Kellokumpu, Kaija Vasala, Juha Kononen, Sanna Ketola, Teijo Kuopio, Kyösti Nuorva
Satakunta Central Hospital	Pia Österlund, Maija-Leena Murashev, Kalevi Pulkkanen, Venla Viitanen, Marko Nieppola, Elina Haalisto
Päijät-Häme Central Hospital	Paul Nyandoto, Aino Aalto
South Pohjanmaa Central Hospital	Timo Ala-Luhtala, Jukka Tuominiemi
Kymenlaakso Central Hospital	Anneli Sainast, Timo Muhonen, Laura Pusa, Sanna Kosonen, Leena Helle, Terhi Hermansson
Kanta-Häme Central Hospital	Riitta Kokko, Laura Aroviita, Petri Nokisalmi
North Karelia Central Hospital	Liisa Sailas, Heikki Tokola
Vaasa Central Hospital	Antti Jekunen, Teemu Pöytäkangas
South Carelia Central Hospital	Kari Möykkynen, Sanna Kosonen, Timo Muhonen
Lapland Central Hospital	Olli-Pekka Isokangas, Svea Vaarala
South Savo Central Hospital	Terhi Hermansson, Tuula Klaavuniemi, Rainer Kolle
Kainuu Central Hospital	Raija Kallio, Peeter Karihtala, Mirja Heikkinen
Central Ostrobothnia Central Hospital	Kaisu Johansson, Anna Sjöstrand, Piia Kajasviita
Länsi-Pohja central hospital	Jaana Kaleva-Kerola
East Savo Central Hospital	Esa Männistö
Åland Central Hospital	Reneé Lindvall-Andersson, Tom Kaunismaa, Pia Vihinen, Nina Cavalli-Björkman

METHODS – STUDY DESIGN AND PARTICIPANTS: POWER CALCULATION

Exact a priori information was not available to be used in sample size calculations. Thus, the sample size calculation was performed in order to get a rough estimate of the required sample size. As guidance to sample size calculation in order to detect a hazard ratio (HR) for death of 0.70 in the resected and/or ablated patient group compared with the no-resection group treated with first-line systemic therapy, with a two-sided type 1 error of 0.05 and type 2 error of 0.20, 671 patients were needed, assuming 2-year mOS in the no-resection group. A 5-year accrual period was planned, with 1% loss-to-survival follow-up was assumed. On the bases of presumed treatment allocation of 25% resected or ablated and 75% treated with systemic therapy, 329 deaths were targeted for the final overall survival analysis.

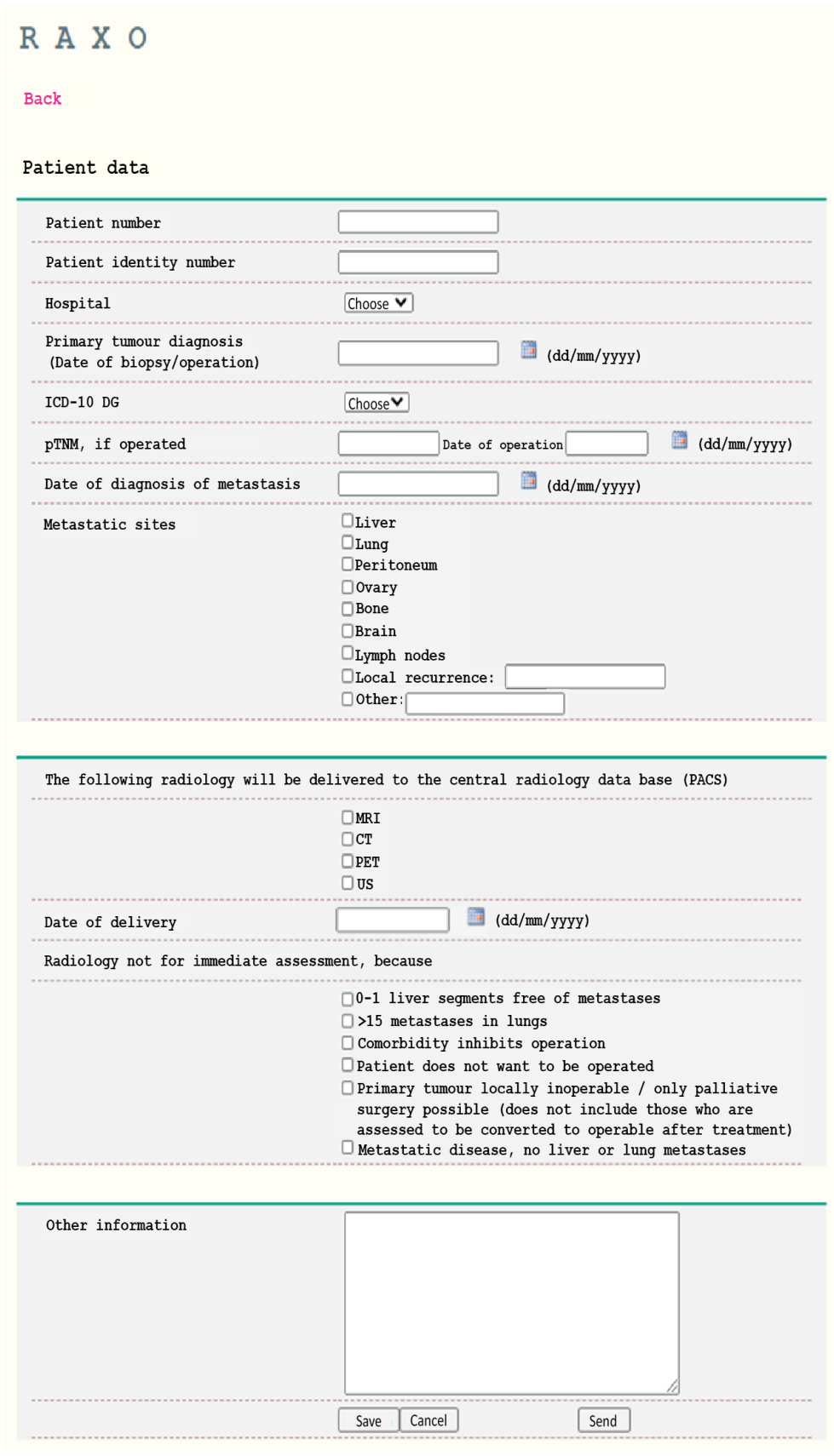
The Finnish Cancer Registry provided population-based data on the incidence and mortality of CRC in each hospital district (Figure 1). An eligibility rate for first-line treatment of 61% was assumed based on Scandinavian data.[29] Recruited proportion per active years of recruitment was calculated for each hospital and approximately 40% of eligible patients were enrolled (Figure 1 and Appendix Table 2).

METHODS – STUDY DESIGN AND PARTICIPANTS: PROTOCOL VIOLATION

Appendix Table 5. Number of centres with protocol violations.

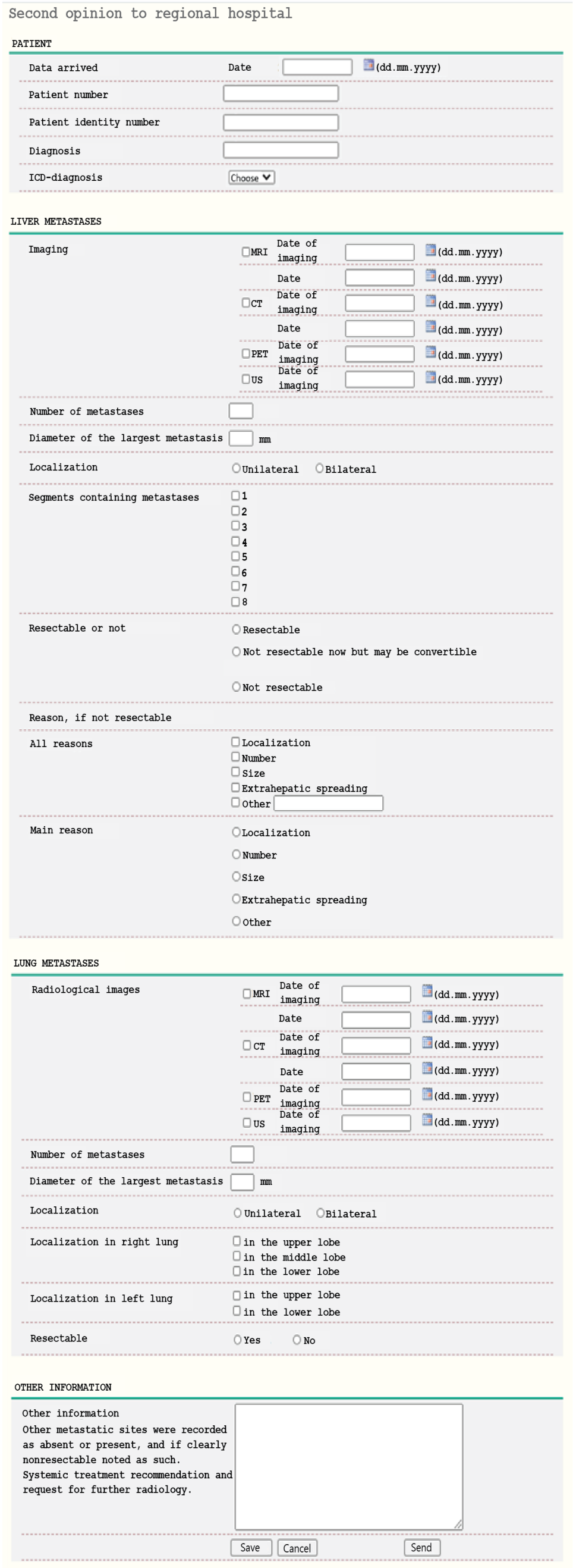
Protocol Violations	N=21
Consent Form - person taking consent appears not to have written own name, signed and/or dated ICF	3
Consent form dates inconsistent	4
Consent after inclusion period -exclusion	1
Correcting of mistakes on ICF not done according to GCP	7
Eligibility deviation - patient exclusion	4
Inadequate maintenance of Delegation Log/CVs	21
Protocol procedure not followed	4
SAE reporting timeframe deviation	21
Trial procedure carried out outside of protocol timeframe	1

METHODS – INTERVENTION: ONLINE INFORMATION FROM LOCAL HOSPITAL



Appendix Figure 1. Patient and tumour characteristics from local hospital provided online via www.raxo.fi for central assessment of resectability.

METHODS – INTERVENTION: ONLINE INFORMATION IN SECOND OPINION



Appendix Figure 2. Repeated second opinion on resectability based on radiology in multidisciplinary team (MDT) assessment at Helsinki tertiary centre provided online via www.raxo.fi to all 21 university and regional hospitals. Treatment decisions were local.

METHODS – INTERVENTION: RADIOLOGY AND SYSTEMIC TREATMENT

The patients underwent scanning with 64-/128-slice CT after intravenous low-osmolar non-ionic contrast (iodine-concentration 350 mgI/ml at 3 ml/sec). Baseline CT included the chest and upper abdomen in the late arterial phase, and abdomen and pelvis in the portal venous phase. Follow-up CT was performed during the portal venous phase. CT scans were reconstructed at 3-mm slices. Board-certified radiologists with 12-31 years of experience and subspecialty in abdominal radiology analysed the images, with consultation of other sub-specialties in radiology, as needed.

Each department used their own standard treatment protocols for systemic therapy based on NCCN and ESMO guidelines.[30-32] Treatment was continued until disease progression, intolerance, or resectability was achieved. In the conversion setting, combination therapy was used, usually a doublet or triplet chemotherapy combined with targeted agents, such as bevacizumab, cetuximab, or panitumumab, according to *RAS*/*BRAF*-status and sidedness.[30-33] In upfront resectable metastases, neoadjuvant and adjuvant oxaliplatin-based chemotherapy was recommended.[34] Adjuvant chemotherapy for 3 months after metastasectomy was recommended based on the physician's discretion.

METHODS – INTERVENTION AND OUTCOMES: RESECTABILITY, RADICALITY AND CLASSIFICATION CRITERIA AND GUARANTEE-TIME BIAS

Liver and lung metastases were separately labelled as resectable, or unresectable (and liver further into borderline) on each assessment. Other metastatic sites were recorded as absent or present and, if clearly non-resectable, noted as such. Peritoneal carcinomatosis was assessed separately at Helsinki or Oulu university hospitals.

Resectability of liver metastases required that negative resection margins could be achieved while preserving at least 30% of the liver volume, so that at least two segments were spared, and that sufficient vascular inflow and outflow and biliary drainage were maintained. Lung metastases were considered resectable if an R0-resection was possible without pulmectomy and patients had no non-resectable extra-thoracic disease. Bilateral metastases were not a contraindication for surgery. In case of peritoneal metastases, the aim of surgical cytoreduction was removal of all visible tumour deposits within the abdominal cavity; multiple peritonectomy procedures and visceral resections were allowed. Other metastases or relapsed primary were considered resectable if surgery with an R0-resection was achievable.

R0 resection was defined as no cancer cells seen microscopically at resection margin, R1 as macroscopically radical resection but cancer cells seen microscopically at the resection margin, and R2 as macroscopic residual tumour seen at surgical specimen or no margin assessed. Patients were classified into the R2 group if later resectable organ was not curatively resected in planned two-to-four staged surgery. Local ablative therapy was grouped in the R2/LAT group as margins cannot be assessed. For cytoreductive surgery the definitions were as follows: R0 = no visible tumour left, R1= tumour deposits under 2.5mm in diameter left, R2= tumour deposits > 2.5 mm left. HIPEC was performed only if R0 or R1 is achieved.

Resection results are not provided separately for R0- and R1-resections as structured pathology reports were not originally harmonised and minimum resection margins were not uniformly reported whereas R2 resections were recorded. In LAT, the histological margins are unknown and thus grouped as R2-resected and/or LAT.

The potential for guarantee-time bias exists when survival is compared across groups defined by an event that is occurring during the follow-up. In this study the event was the resection due to re-assessment of resectability after conversion therapy. The survival times of patients with resection after conversion or neoadjuvant therapy vs. patients with upfront resection and systemic therapy only/best supportive care only groups were not comparable. For the patients with resection after conversion the total survival time is the time before resection plus the time after resection. The length of the former time may cause bias. Conditional landmark analysis was used for OS to control the bias and the fixed time of 12 months landmark was selected. The patients still in the study at 12 months were divided into categories as allocated within first 12 months and the follow-up time starts from the new zero, thus 100% for all four arms at 12 months.

METHODS AND RESULTS – DEMOGRAPHICS AND ADJUSTED MULTIVARIABLE ANALYSIS FOR PRECEDURES OR NOT

Essential patient characteristics according to the consensus statement by Goey et al 2018[35] were used for demographics and in the adjusted cox-model for procedures i.e. R0/1/2-resection and/or local ablative therapy (LAT).

Appendix Table 6. Essential patient characteristics by procedure i.e. resection and/or local ablative therapy (LAT) or not i.e. "systemic therapy alone" or best supportive care (BSC).

		All patients		R0-1 resection		R2-resection and/or LAT		Systemic therapy alone	
		1063	100%	326	73%	73	7%	664	61%
Age	<70	708	67%	239	73%	51	70%	418	63%
	≥70	355	33%	87	27%	22	30%	246	37%
ECOG	PS 0	295	28%	140	43%	19	26%	136	21%
	PS 1-3	768	72%	186	57%	54	74%	528	80%
Primary tumour location	Right colon	300	28%	73	22%	13	18%	214	33%
	Left colon	394	37%	142	44%	34	47%	218	33%
	Rectum	363	34%	111	34%	26	36%	226	34%
Primary tumour resection	Operated upfront	720	68%	274	84%	50	69%	396	60%
	Not operated	343	32%	52	16%	23	32%	268	40%
Prior adjuvant chemotherapy	No	727	68%	178	55%	46	63%	503	76%
	Adjuvant chemotherapy	336	32%	148	45%	27	37%	161	24%
Number of metastatic sites	1	576	54%	278	85%	31	43%	267	40%
	2 to 6	487	46%	48	15%	42	58%	397	60%
Liver only metastases	Yes	640	60%	90	28%	47	64%	503	76%
	No	423	40%	236	72%	26	36%	161	24%
Liver involvement	<25%	261	25%	156	48%	23	32%	82	12%
	≥25%	531	50%	106	33%	33	45%	392	59%
	No liver metastases	271	26%	64	20%	17	23%	190	29%
Presentation	Synchronous	715	67%	186	57%	45	62%	484	73%
	Metachronous	348	33%	140	43%	28	38%	180	27%
RAS status	*KRAS*/*NRAS* wildtype	507	49%	165	52%	25	35%	317	49%
	KRAS/*NRAS* mutant	533	51%	151	48%	46	65%	336	52%
BRAF status	*BRAF* wildtype or not tested	810	90%	264	96%	59	95%	487	87%
	BRAF mutant	88	10%	12	4%	3	5%	73	13%
Mismatch repair status¶	pMMR	299	96%	102	31%	19	26%	178	27%
	dMMR	14	4%	7	2%	0	0%	7	1%
	Not tested	750	··	217	··	54	··	479	··

BSC= best supportive care only; dMMR= deficient mismatch repair, ECOG = *Eastern Cooperative Oncology Group;* LAT = local ablative therapy; *pMMR= proficient mismatch repair; PS= performance status*
¶ Proportions of total number of tested for MMR status

Appendix Table 7. Multivariable analysis according to essential patient characteristics for OS from mCRC diagnosis for procedures versus not.

		HR	95% confidence interval	
Procedure	Resection and/or LAT vs Not	0·21	0·15	0·28
Age	≤70 vs >70	0·92	0·74	1·14
ECOG	PS 0 vs1 to 3	0·63	0·49	0·80
Primary tumour location	Right colon	1·00	··	··
	Left colon	0·58	0·44	0·76
	Rectum	0·52	0·39	0·68
Primary tumour resection	Upfront surgery vs No surgery	0·52	0·40	0·67
Prior adjuvant chemotherapy	Yes vs No	0·74	0·55	0·99
Number of metastatic sites	1 vs 2–6	0·57	0·38	0·85
Liver only metastases	Yes vs No	0·62	0·38	1·00
Liver involvement	< 25%	1·00	··	··
	≥ 25%	1·17	0·86	1·58
	No liver metastases	0·94	0·63	1·41
Presentation	Metachronous vs Synchronous	1·03	0·73	1·45
RAS status	Wildtype vs Mutant	0·69	0·55	0·86
BRAF status	Wildtype vs Mutant	0·42	0·31	0·58
Mismatch repair status	pMMR	1·00	··	··
	dMMR	0·61	0·27	1·35
	Not tested	1·09	0·88	1·36

dMMR= deficient mismatch repair, ECOG = Eastern Cooperative Oncology Group; LAT = local ablative therapy; pMMR= proficient mismatch repair; PS= performance status

Appendix Table 8. Multivariable analysis according to according to grade, stage, primary location and metastatic sites for OS from mCRC diagnosis for procedures versus not.

		HR	95% confidence interval	
Procedure	Resection and/or LAT vs Not	0.20	0.17	0.25
Age	<70 vs ≥70 years	0.81	0.69	0.95
Sex	Male vs Female	1.01	0.87	1.17
Primary tumour location	Right colon	1.00		
	Left colon	0.70	0.58	0.84
	Rectum	0.63	0.53	0.76
Metastatic sites	Liver	1.59	1.30	1.93
	Lung	1.12	0.95	1.31
Grade	Grade 1	1.00		
	Grade2	1.34	1.02	1.76
	Grade 3	2.21	1.61	3.02
	Grade unknown	1.86	1.38	2.53
T-stage	T1	1.00		
	T2	1.17	0.46	2.98
	T3	1.25	0.53	2.96
	T4	1.36	0.56	3.26
	T unknown	1.25	0.34	4.61
N-stage	N0	1.00		
	N1	1.08	0.87	1.35
	N2	1.42	1.16	1.73
	N unknown	2.45	1.60	3.76
Presentation ǂ	Synchronous	1.00		
	Early metachronous	1.068	0.817	1.396
	Late metachronous	0.911	0.74	1.123

ǂ early metachronous from diagnosis to 12 months and late metachronous more than 12 months from colorectal cancer diagnosis. HR = hazard ratio.

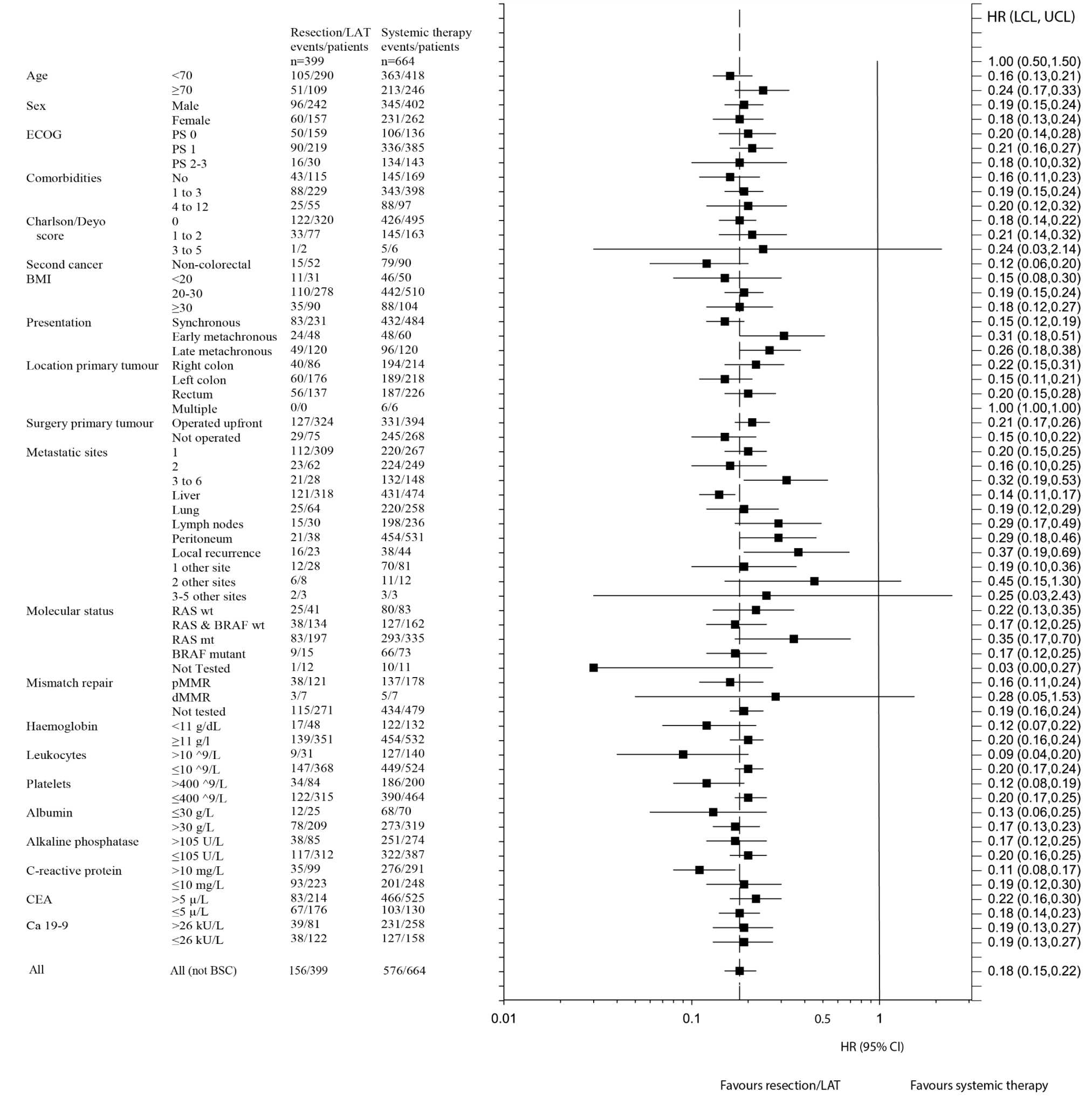
RESULTS – DETAILED DEMOGRAPHICS FOR R0/1-RESECTION, R2/LAT, "SYSTEMIC THERAPY ONLY" AND BEST SUPPORTIVE CARE

Appendix Table 9. Detailed baseline demographics separated for treatment groups.

		Total		R0/1-resection		R2-resection & LAT		Systemic therapy only		Best supportive care	
		1086	100%	326	30%	73	7%	664	61%	23	1%
Age	Median (range)	66·4	(24-90)	64·8	(25-84)	66·5	(42-82)	67	(24-89)	73·4	(52-90)
	<70	715	66%	239	73%	51	70%	418	63%	7	30%
	≥70	371	34%	87	27%	22	30%	246	37%	16	70%
Sex	Male	656	60%	199	61%	43	59%	402	61%	12	52%
	Female	430	40%	127	39%	30	41%	262	40%	11	48%
ECOG	PS 0	295	27%	140	43%	19	26%	136	21%	0	0%
	PS 1	600	55%	166	51%	44	60%	385	58%	5	22%
	PS 2-3	191	18%	20	6%	10	14%	143	22%	18	78%
Comorbidities	No	289	27%	97	30%	18	25%	169	26%	5	22%
	1 to 3	643	59%	188	58%	41	56%	398	60%	16	70%
	4 to 12	154	14%	41	13%	14	19%	97	15%	2	9%
Charlson/Deyo	0	834	77%	262	80%	58	80%	495	75%	19	83%
score	1 to 2	244	23%	62	19%	15	21%	163	25%	4	17%
	3 to 5	8	1%	2	1%	0	0%	6	1%	0	0%
Second cancer	Non-colorectal	143	13%	46	14%	6	8%	90	14%	1	4%
BMI	<20	84	8%	25	8%	6	8%	50	8%	3	13%
	20-29·9	802	74%	228	70%	50	69%	510	77%	14	61%
	≥30	200	18%	73	22%	17	23%	104	16%	6	26%
Presentation‡	Synchronous	736	68%	186	57%	45	62%	484	73%	21	91%
	Early metachronous	109	10%	38	12%	10	14%	60	9%	1	4%
	Late metachronous	241	22%	102	31%	18	25%	120	18%	1	4%
Primary tumour location	Right colon	310	29%	73	22%	13	18%	214	32%	10	44%
	Left colon	396	37%	142	44%	34	47%	218	33%	2	9%
	Rectum	374	34%	111	34%	26	36%	226	34%	11	48%
	Multiple	6	1%	0	0%	0	0%	6	1%	0	0%
Primary tumour resection‡	Upfront surgery	728	67%	274	84%	50	69%	398	60%	6	26%
	No surgery	358	33%	52	16%	23	32%	266	40%	17	74%
Prior adjuvant	No adjuvant	124	35%	46	33%	10	36%	66	37%	2	100%
chemotherapy†	Fluoropyrimidine	99	28	34	24%	7	25%	58	32%	0	0%
	Oxaliplatin-based	127	36%	60	43%	11	39%	56	31%	0	0%
Radiotherapy	No	238	64%	50	45%	16	62%	163	72%	9	82%
for rectal¥	Preop. 5x5Gy	53	14%	31	28%	5	19%	17	8%	0	0%
	Preop. chemoradiation	64	17%	28	25%	3	12%	33	15%	0	0%
	Palliative radiotherapy	19	5%	2	2%	2	8%	13	6%	2	18%
Number of metastatic sites	1	586	54%	278	85%	31	43%	267	40%	10	44%
	2	319	29%	36	11%	26	36%	249	38%	8	35%
	3 to 6	181	17%	12	4%	16	22%	148	22%	5	22%
Site of metastases	Liver	812	75%	262	80%	56	77%	474	71%	20	87%
	Lung	330	31%	37	12%	27	37%	258	39%	8	35%
	Lymph nodes	275	25%	15	5%	15	21%	236	36%	9	39%
	Peritoneum	175	16%	26	8%	12	16%	133	20%	4	17%
	Local recurrence	67	6%	14	4%	9	12%	44	7%	0	0%
	1 other site	110	10%	19	6%	9	12%	81	12%	1	4%
	2 other sites	20	2%	6	2%	2	3%	12	2%	0	0%
	3-5 other sites	6	1%	1	0%	2	3%	3	1%	0	0%
Molecular status §	RAS wild-type	127	12%	35	11%	6	8%	83	13%	3	15%
	RAS & BRAF wild-type	301	28%	118	37%	16	23%	162	25%	5	25%
	RAS mutant	539	51%	151	48%	46	65%	335	51%	7	35%
	BRAF mutant	93	9%	12	4%	3	4%	73	11%	5	25%
Mismatch repair status¶	pMMR	302	95%	102	94%	19	100%	178	96%	3	75%
	dMMR	15	5%	7	6%	0	0%	7	4%	1	25%
Haemoglobin	<11 g/dL	188	17%	40	12%	8	11%	132	20%	8	35%
Leukocytes	>10 ^9/L	185	17%	25	8%	6	8%	140	21%	14	61%
Platelets	>400 ^9/L	292	27%	69	21%	15	21%	200	30%	8	35%
Albumin #	<30 g/L	104	16%	19	10%	6	14%	70	18%	9	60%
Alkaline phosphatase #	>105 U/L	373	35%	68	21%	17	23%	274	41%	14	70%
C-reactive protein #	>10 mg/L	409	46%	79	30%	20	33%	291	54%	19	86%
CEA #	>5 µ/L	758	71%	169	53%	45	64%	525	80%	19	86%
Ca 19-9 #	>26 kU/L	345	55%	65	39%	16	44%	258	62%	6	50%

*Patients were divided into four groups: curative resection (R0-1), R2 resection of metastases or primary, Local Ablative Therapy (LAT) or not all tumour sites resected curatively (R2/LAT); systemic therapy only or best supportive care only (BSC) group.
ǂ early metachronous from diagnosis to 12 months and late metachronous more than 12 months from colorectal cancer diagnosis.
‡ Upfront surgery in synchronous or metachronous
BMI = body mass index; CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; dMMR= deficient mismatch repair, pMMR= proficient mismatch repair; ECOG = *Eastern Cooperative Oncology Group;* LAT = local ablative therapy; *Preop= preoperative; PS= performance status.*
Data are n (%) unless otherwise specified. † Proportions of total number of metachronous. ¥ Proportions of total number of rectal cancers. § Proportions of total number tested for molecular status. ¶ Proportions of total number of tested for MMR status. # Proportions of total number with laboratory test performed.

RESULTS – FOREST PLOT OF SUBGROUP ANALYSES FOR OVERALL SURVIVAL IN PROCEDURES VERSUS NOT



BSC = best supportive care, HR = hazard ratio, CI = confidence interval.

Appendix Figure 3. Forest plot of subgroup analyses of overall survival. Data shown for patients resected and/or ablated or receiving systemic therapy alone (best supportive care patients excluded).

METHODS AND RESULTS – DEMOGRAPHICS AND ADJUSTED MULTIVARIABLE ANALYSIS FOR R0/1-RESECTION, R2/LAT, SYSTEMIC THERAPY ONLY AND BEST SUPPORTIVE CARE

Essential patient characteristics according to the consensus statement by Goey et al 2018[35] were used for demographics and in the adjusted cox-model for overall survival from mCRC diagnosis in R0/1-resected, R2-resected and/or local ablative therapy (LAT), and "Systemic therapy only" groups, but Best supportive care group is omitted.

Appendix Table 10. Multivariable analysis according to essential patient characteristics for OS from mCRC diagnosis for R0/1-resection, R2-resection and/or LAT, "Systemic therapy alone" versus Best supportive care.

		HR	95% confidence interval	
Resection and/or LAT	"Systemic therapy alone"	1·00	··	··
	R0/1-resection	0·16	0·11	0·23
	R2 and/or LAT	0·47	0·30	0·73
	Best supportive care	46·9	21·9	100·5
Age	<70 vs ≥70	0·99	0·79	1·23
ECOG	PS 0 vs1 to 3	0·64	0·50	0·82
Primary tumour location	Right colon	1·00	··	··
	Left colon	0·58	0·44	0·76
	Rectum	0·49	0·37	0·65
Primary tumour resection	Upfront surgery vs No surgery	0·54	0·42	0·69
Prior adjuvant chemotherapy	Yes vs No	0·66	0·49	0·89
Number of metastatic sites	1 vs 2 to 6	0·56	0·37	0·83
Liver only metastases	Yes vs No	0·61	0·38	0·99
Liver involvement	No liver metastases	0·89	0·60	1·34
	< 25%	1·00	··	··
	≥25%	1·13	0·84	1·53
Presentation	Metachronous vs Synchronous	0·97	0·69	1·37
RAS status	Wildtype vs Mutant	0·67	0·54	0·84
BRAF status	Wildtype vs Mutant	0·43	0·31	0·60
Mismatch repair status	pMMR	1·00	··	··
	dMMR	0·54	0·24	1·20
	Not tested	1·09	0·87	1·35

dMMR= deficient mismatch repair, ECOG = Eastern Cooperative Oncology Group, HR = Hazard ratio, LAT = local ablative therapy, pMMR= proficient mismatch repair; PS= performance status.

Appendix Table 11. Multivariable analysis according to grade, stage, primary location, presentation, and metastatic sites for OS from mCRC diagnosis for R0/1-resection, R2-resection and/or LAT, "Systemic therapy alone" versus Best supportive care.

		HR	95% confidence interval	
Resection and/or LAT	"Systemic therapy alone"	1.00	··	··
	R0/1-resection	0.16	0.13	0.21
	R2 and/or LAT	0.43	0.31	0.59
	Best supportive care	15.40	9.57	24.78
Age	<70 vs ≥70 years	1.15	0.98	1.34
	Male vs Female	0.96	0.83	1.12
Primary tumour location	Right colon	1.00	··	··
	Left colon	0.68	0.57	0.82
	Rectum	0.59	0.49	0.71
Metastatic sites	Liver	1.62	1.33	1.96
	Lung	1.10	0.94	1.30
Differentiation	Grade 1	1.00	··	··
	Grade2	1.32	1.00	1.73
	Grade 3	2.18	1.59	2.99
	Grade unknown	1.74	1.28	2.36
T-stage	T1	1.00	··	··
	T2	1.09	0.43	2.78
	T3	1.10	0.46	2.61
	T4	1.19	0.50	2.88
	T unknown	1.09	0.30	4.01
N-stage	N0	1.00	··	··
	N1	1.03	0.83	1.29
	N2	1.38	1.13	1.68
	N unknown	2.33	1.52	3.59
Presentation ǂ	Synchronous	1.00	··	··
	Early metachronous	1.09	0.83	1.42
	Late metachronous	0.92	0.75	1.13

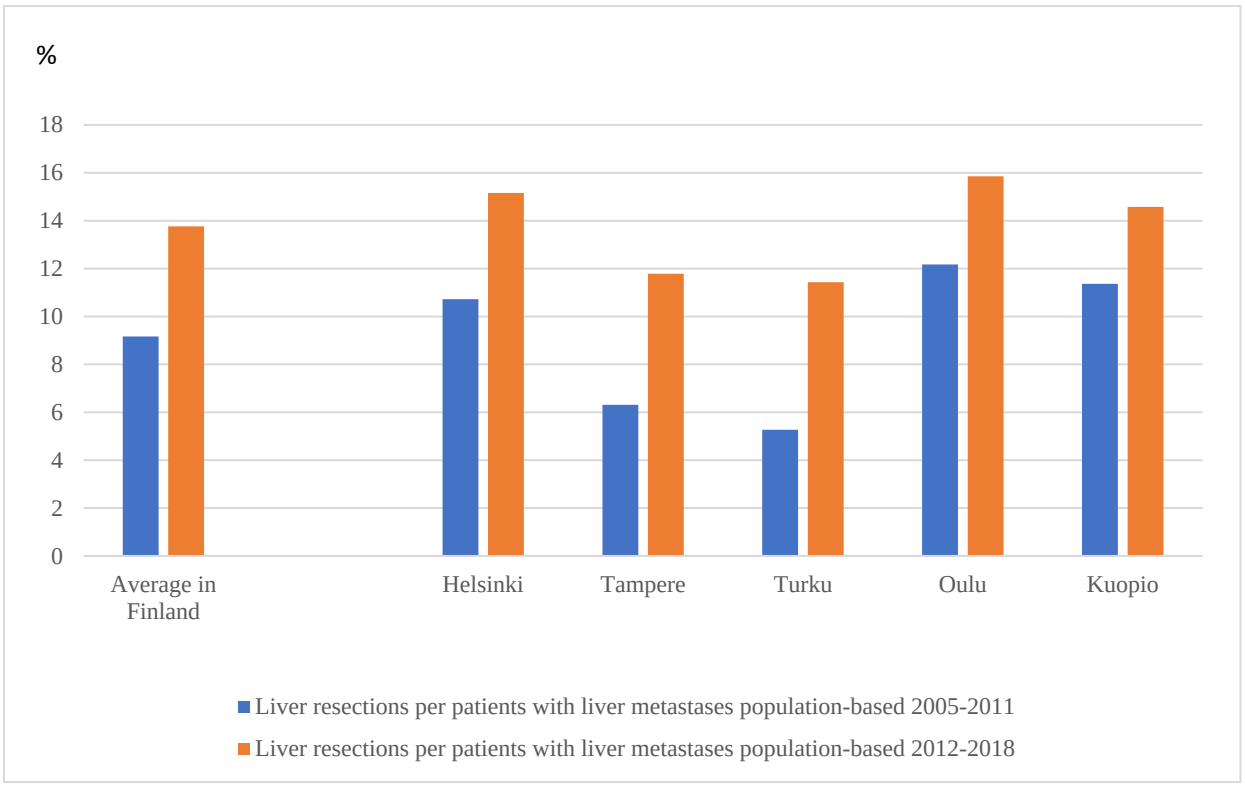
ǂ early metachronous from diagnosis to 12 months and late metachronous more than 12 months from colorectal cancer diagnosis. HR = Hazard ratio, LAT = local ablative therapy.

METHODS AND RESULTS – POPULATION-BASED LIVER RESECTION RATE ESTIMATES

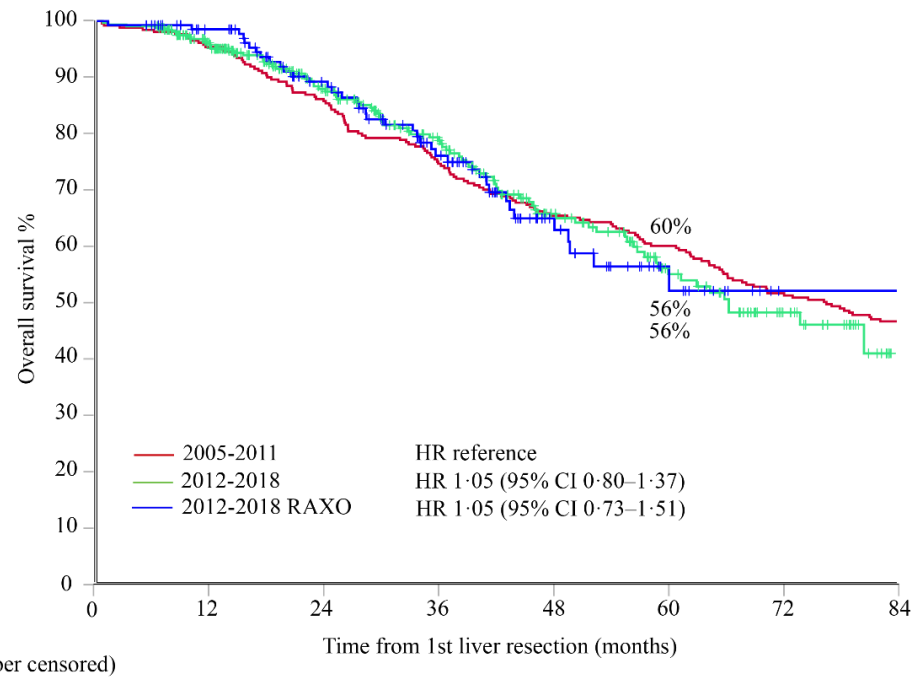
Liver resection rates were recorded according to the subprotocol for the RAXO data collection trial (study protocol Appendix page 20-42). Resection data at all hospitals were not available electronically for other resections (e.g. lung, peritoneal, ovary, local relapse) than liver resections, and these will be retrieved later, some manually. Nationwide liver resection rates were retrieved from electronic registries (n=4 hospitals, with slight risk for underestimation) or reliable liver resection registries (n=2 hospitals) at all six hospitals performing liver resections (with Nordic classification of surgical procedures code JJB/JJA and ICD-10 C18, C19, or C20). Resected cases are coded to their own district regardless of the location of the hospital where the resection was performed. Helsinki performs all resections for 54% of the Finnish population (1.97/5.54 million inhabitants). To control for migration and increasing CRC incidence at the five university hospital districts, these resections were compared with cancer-registry derived population-based numbers for mCRC cases (reliable numbers for deaths due to CRC from the Finnish Cancer Registry were used instead of estimates of the number of mCRC cases, thus, slightly underestimating the number of mCRC cases) per hospital district and year. Individual patient data were provided by the Finnish Cancer Registry and Statistics Finland based on permission THL/2305/5.05.00/2019 and TK-53-733-20. The rate of liver metastases in mCRC is estimated to be 75% based on the RAXO data with 1086 Finnish patients and data from 21,214 study patients.[21]

During the RAXO inclusion period (2012-2018), 938 liver resections were performed nationwide and 447 in the preceding 7 years (2005-2011), with a crude estimated increase of +109%. The population-based liver resection rates increased from 9% to 14% among estimated mCRCs with liver involvement, when comparing the preceding seven years (2005-2011) to the RAXO inclusion years (2012-2018; Appendix Figure 3). The liver resections rate was 12% for patients not included in the RAXO study 2012-2018. Referrals for performed liver resection from the four university hospitals to Helsinki tertiary centre increased from 10 to 36 (+260%) when comparing the two 7-year periods. Regional differences diminished during the RAXO time period with largest improvements in the Tampere and Turku university districts (Appendix Figure 3).

Overall survival from 1st liver resection for patients (n=260+328+142) operated at Helsinki university hospital is presented in Appendix Figure 4. Median OS was 76 months for patients resected in the preceding 7 years (2005-2011), and in 2011-2018 66 months for non-RAXO patients and not reached for RAXO-patients.



Appendix Figure 4. Population-based liver resection rates nationwide in Finland and separately for the five university hospital districts during the RAXO inclusion period (2012-2018) and preceding seven years (2005-2011) among all estimated cases with liver metastases from colorectal cancer.



Number at risk (number censored)

2005-2011	260 (0)	248 (0)	223 (0)	194 (0)	170 (0)	156 (0)	134 (0)	121 (97)
2011-2018 non-RAXO	328 (42)	273 (106)	190 (139)	139 (172)	85 (193)	53 (213)	26 (237)	0 (237)
2011-2018 RAXO	142 (14)	126 (33)	96 (50)	66 (76)	32 (91)	13 (102)	1 (103)	0 (103)

Appendix Figure 5. Overall survival from 1st liver resection in patients operated at Helsinki university hospital during RAXO era and preceding 7 years.

METHODS AND RESULTS – POPULATION-BASED RESULTS

Appendix Table 12. RAXO baseline characteristics and outcomes in comparison with population-based data for Scandinavian, Dutch and Finnish cohorts.

Reference	RAXO study		RAXO and Sorbye et al	Sorbye et al 2009 (data on file)	Sorbye et al (data on file)	Hamers et al. Int J Cancer 2020	RAXO Tampere university hospital	RAXO Turku university hospital
Population	Real-world		Real-world Population	Population	Population	Population	Population	Population
Unselected vs Selected population	Unselected for treatable		Unselected	Unselected	Unselected	Unselected	Unselected	Unselected
Single-site vs multisite metastases	Multisite		Multisite	Yes	Multisite	Multisite	Multisite	Multisite
Prospective vs retrospective	Prospective		Prospective		Prospective	Retrospective	Retrospective	Retrospective
Study name	**RAXO**		RAXO and PRCRC	**PRCRC**	**PRCRC BSC excluded**	**Dutch population based**	**Finnish population based**	**Finnish population based**
Treatment arm or study population	**Resection, systemic BSC excluded**	**Resection, systemic, BSC**	**BSC only**	**Resection, systemic, BSC**	**Resection, systemic**	**Resection, systemic, BSC**	**Resection, systemic, BSC**	**Resection, systemic., BSC**
Inclusion period	**2012-2018**	**2012-2018**	**2003-2018**	**2003-2006**	**2003-2006**	**2008-2016**	**2011-2018**	**2011-2018**
Number of patients	1063	1086	316	798	503	27,275	866	716
Target population	mCRC		mCRC BSC	All mCRC	Treatable mCRC	Synchronous mCRC	All mCRC	All mCRC
Age, median (range)	66 (24-89)	66 (24-90)	78 (40-97)	71 (22-97)	65 (22-92)	69 (··)	70 (24-97)	70 (28–94)
Elderly (>70 years if not noted otherwise)	34 %	34 %	82 %	53 %	36 %	49 %	51 %	48 %
Male gender	61 %	60 %	49 %	52 %	55 %	56 %	56 %	57 %
PS 0	28 %	27 %	5 %	31 %	46 %	43 %		
PS 1	57 %	57 %	24 %	49 %	39 %			
PS 2-3	15 %	16 %	71 %	20 %	15 %	9 %		
Single-site metastases	48 %	47 %	30 %	35 %	36 %	62 %		
Median number metastatic sites	2	2	2	2	2	1		
Synchronous metastases	67 %	68 %	61 %	54 %	52 %	100 %	63 %	
Liver metastases	75 %	75 %	64 %	65 %	67 %	75 %		
Liver only	34 %	34 %	15 %	17 %	18 %	43 %		
Lung metastases	30 %	31 %	27 %	27 %	28 %	24 %		
Lung only	6 %	6 %	3 %	4 %	5 %	5 %		
Lymph node metastases	25 %	25 %	23 %	27 %	30 %			
Lymph nodes only	3 %	3 %	2 %	3 %	4 %			
Peritoneal metastases	16 %	16 %	21 %	18 %	17 %	22 %		
Peritoneal only	4 %	4 %	3 %	2 %	2 %	9 %		
Ovarian	6 %	6 %						
Ovarian-only	0 %	0 %						
Local relapse	6 %	6 %	6 %	5 %	5 %			
Local relapse-only	1 %	1 %	3 %	1 %	1 %			
Rectal primary tumour	34 %	34 %	24 %	32 %	37 %	28 %	42 %	38 %
Colon primary tumour	66 %	66 %	76 %	68 %	63 %	68 %	58 %	62 %
Right colon	29 %	29 %	44 %	36 %	31 %	35 %	22 %	31 %
Left colon	37 %	37 %	32 %	31 %	32 %	33 %	34 %	24 %
Primary tumour resection	62 %	62 %	63 %	72 %	76 %		47 %	
Prior radiotherapy for primary tumour	13 %	13 %	7 %	11 %	13 %			
Prior adjuvant therapy for primary tumour	32 %	32 %	3 %	11 %	16 %			
KRAS / RAS wild-type (+/- BRAF wt)	41 %	41 %	37 %	0 %	41 %	52 %		
RAS+BRAF wild-type	29 %	29 %	35 %	39 %	41 %			
KRAS ± NRAS mutant	51 %	50 %	41 %	41 %	40 %	48 %		
BRAFV600E mutant	8 %	9 %	22 %	20 %	19 %	15 %		
Deficient mismatch repair	4 %	5 %		8 %		6 %		
Resectability rate upfront	29 %	28 %						
Response rate to systemic therapy	61 %	59 %		39 %	39 %			
Conversion rate	13 %	13 %						
Resection rate R0-1	31 %	30 %	0 %	6 %	10 %			
Resection rate R0-2	36 %	35 %	0 %			6-11%	18 %	8 % ₣
Local ablative therapy	2 %	2 %	0 %					5 % ₣
Systemic therapy	100 %	98 %	0 %	52 %	100 %	56 %	66 %	55 %
Best supportive care	0 %	2 %	100 %	42 %	0 %	22 %	31 %	42 %
Pre-metastasectomy chemotherapy	79 %	74 %	0 %					
Post-metastasectomy adjuvant therapy	81 %	81 %	0 %	14 %	14 %			
Perioperative therapy	62 %	62 %	0 %					
OS (months) all	31 (IQR 16–64)	30 (IQR 15–62)	3 (IQR 2–8)	10 (IQR 3–22)	16 (IQR 9–32)	12 (IQR 3-25)*	16 (IQR 5–41)	16 (5–42)
OS (months) resected	71 (IQR 39–141)	71 (IQR 39–141)		61 (IQR 34–··)	61 (IQR 34–··)	48 (IQR 26–··)*	65 (IQR 34–··)	79 (IQR 35– ··)
OS (months) systemic (only)	21 (IQR 12–34)	21 (IQR 12–34)		15 (IQR 8–27)	15 (IQR 8–27)	15 (IQR 6–34)*	22 (IQR 11–42)	22 (IQR 11–42)
OS (months) BSC	··	3 (IQR 2–3)	3 (IQR 2–8)	3 (IQR 2–8)		2 (IQR 2-4)*	3 (IQR 1–8)	6 (IQR 1-20)¥
OS 1/3/5-year rate - resected	98/77/61%	98/77/61%		98/71/55%	98/71/55%		95/73/53%	95/75/67%
OS 1/3/5-year rate all	83/43/28%	83/42/27%	15/2/1%	44/11/6%	65/19/10%		72/29/13%	59/28/20%
PFS (months)	13 (IQR 8–26)	13 (IQR 7–25)		11 (IQR 6–17)	11 (IQR 6–17)			
HR systemic therapy alone		Ref		Ref	Ref		Ref	Ref
HR resection		0·15 (0·12–0·19)		0·25 (0·18–0·36)	0·25 (0·18–0·36)		0·30 (0·24–0·39)	0·24 (0·14–0·42)
HR Local ablative therapy		0·39 (0·29–0·53)						0·62 (0·39–0·98)
HR BSC		14·2 (9·2–22·0)		3·26 (2·80–3·80)	3·26 (2·80–3·80)		6·17 (5·14–7·41)	1·78 (1·50–2·12)¥

BSC = best supportive care, * estimate from figures, ¥ non-verified data for BSC. **₣ = liver and lung procedures.**
Sorbye et al[29], Hamers et al[36]

RESULTS – SURGERY AND SYSTEMIC THERAPY FOR ALL AND SINGLE METASTATIC SITES

Appendix Table 13. Metastatic sites during trajectory, systemic therapy and resections/LAT for all patients and per single-site metastases divided as liver, lung, peritoneal and other single-site.

		All patients		All single-site		Liver-limited		Lung-limited		Peritoneal-limited		Other single-site*	
		1086		586	100%	430	73%	66	11%	45	8%	45	8%
Metastatic sites during trajectory													
Metastatic sites	1	266	24%	266	45%	193	45%	36	55%	18	40%	19	42%
	2	322	30%	159	27%	120	28%	17	26%	10	22%	12	27%
	3 to 9	498	46%	161	28%	117	27%	13	20%	17	38%	14	31%
New metastatic sites													
Liver	Trajectory	867	80%	464	79%	..	..	12	18%	8	18%	14	31%
Lung	Trajectory	571	53%	245	42%	162	38%	..	..	8	18%	9	20%
Peritoneum	Trajectory	280	26%	101	17%	50	12%	1	2%	..	..	5	11%
Lymph nodes	Trajectory	462	43%	158	27%	110	26%	5	8%	12	27%	31	69%
Local relapse	Trajectory	105	10%	33	6%	14	3%	4	6%	3	7%	12	27%
1-4 other sites	Trajectory	136	13%	9	2%	76	18%	19	29%	15	33%	16	36%
Surgery and systemic therapy													
Resection status	Resectable & R0-1 resected	230	21%	196	33%	157	60%	25	93%	8	73%	6	67%
	Resectable & R2 or LAT	35	3%	19	14%	15	6%	2	7%	2	18%	0	0%
	Converted & R0-1 resected	96	9%	82	3%	79	30%	0	0%	1	9%	2	22%
	Converted & R2 or LAT	38	3%	12	2%	11	4%	0	0%	0	0%	1	11%
	Not resected	687	63%	277	47%	168	39%	39	59%	34	76%	36	80%
First line therapy	Comb. CT & anti-EGFR	139	13%	87	15%	81	19%	4	6%	1	2%	5	11%
	Comb. CT & anti-VEGF	550	51%	283	48%	206	49%	29	45%	25	57%	24	55%
	Comb. CT (no biologic)	224	21%	132	23%	97	23%	20	31%	10	23%	5	11%
	Single CT +/- anti-VEGF/-EGFR	147	14%	71	12%	37	9%	11	17%	8	18%	10	23%
	No systemic therapy	26	2%	13	2%	9	2%	2	3%	1	2%	1	2%
First resection §	Conversion (+ adjuvant)	140 (87)	35%	103 (69)	22%	95 (64)	36%	4 (1)	15%	1 (1)	9%	3 (3)	33%
	Neoadjuvant (+ adjuvant)	157 (116)	39%	133 (105)	24%	119 (99)	45%	11 (6)	41%	1 (0)	9%	2 (0)	22%
	Adjuvant	60	15%	24	19%	35	13%	10	37%	5	46%	2	22%
	Only resection	42	11%	21	35%	13	5%	2	7%	4	36%	2	22%
Second resection ¶	Conversion (+ adjuvant)	44 (24)	28%	24 (15)	22%	19 (12)	21%	2 (1)	18%	3 (1)	50%	0	0%
	Neoadjuvant (+ adjuvant)	33 (20)	21%	26 (15)	24%	25 (24)	28%	0	0%	1 (1)	17%	0	0%
	Adjuvant	28	18%	20	19%	14	16%	5	46%	1	17%	0	0%
	Only resection	50	32%	38	35%	32	36%	4	36%	1	17%	1	100%
Systemic therapy	Disease control intent	888	82%	426	73%	297	69%	52	79%	40	89%	37	82%
	Only curative treatment	175	16%	150	24%	126	29%	13	20%	4	9%	7	16%
	Best supportive care only	23	2%	10	2%	7	2%	1	2%	1	2%	1	2%
Best response	CR/NED	98	9%	78	13%	58	13%	9	14%	4	9%	7	16%
	PR	555	51%	308	53%	241	56%	29	44%	12	27%	26	58%
	SD	294	27%	144	25%	96	22%	24	36%	19	42%	5	11%
	PD	126	12%	49	8%	31	7%	3	5%	9	20%	6	13%
	Not evaluated	13	1%	7	1%	4	1%	1	2%	1	2%	1	2%
Primary	Never operated	253	23%	88	15%	66	15%	7	11%	11	24%	4	9%
	Upfront	726	67%	429	73%	306	71%	55	83%	33	73%	35	78%
	During therapy	107	10%	69	12%	58	14%	4	6%	1	2%	6	13%
Primary radicality #	R0	763	92%	467	94%	347	95%	53	90%	28	82%	39	95%
	R1	41	5%	20	4%	13	4%	4	7%	2	6%	1	2%
	R2	29	3%	11	2%	4	1%	2	3%	4	12%	1	2%
Number resections & LAT †	Cases with 1 procedure	254	63%	211	68%	181	69%	15	56%	5	45%	8	73%
	Cases with 2 procedures	95	24%	66	21%	57	22%	8	30%	2	18%	1	9%
	Cases with 3 to 11 procedures	52	13%	33	11%	24	9%	4	15%	4	36%	0	0%
Resection radicality †	R0	336	81%	270	85%	231	87%	26	96%	6	46%	7	64%
	R1	41	10%	27	9%	21	8%	1	4%	3	23%	2	18%
	R2	36	9%	20	6%	14	5%	0	0%	4	31%	2	18%
Resections by metastatic site													
Liver resection and/or LAT	Number of cases	316	29%	263	45%	260	60%	1	2%	1	2%	1	0·3%
	1 procedure †	243	77%	201	76%	199	77%	0	0%	1	100%	1	100%
	2 procedures †	53	17%	45	17%	44	17%	1	100%	0	0%	0	0%
	3 to 5 procedures †	20	6%	17	6%	17	7%	0	0%	0	0%	0	0%
Lung resection and/or LAT	Number of cases	81	7%	59	10%	32	7%	27	41%	0	0%	0	0%
	1 procedure †	62	77%	47	80%	27	84%	20	74%	0	0%	0	0%
	2 to 9 procedures †	19	23%	12	20%	5	16%	7	26%	0	0%	0	0%
Cytoreductive surgery +/- HIPEC	Number of cases	48	4%	20	3%	8	2%	0	0%	11	24%	1	0·3%
	1 procedure †	40	83%	15	75%	7	88%	0	0%	7	64%	1	100%
	2 procedures †	8	17%	5	25%	1	13%	0	0%	4	36%	0	0%
Local relapse surgery	Number of cases	41	4%	12	2%	5	1%	2	3%	1	2%	4	1%
	1 procedure †	35	85%	10	83%	4	80%	1	50%	1	100%	4	100%
	2 procedures †	6	15%	2	17%	1	20%	1	50%	0	0%	0	0%
Distant lymphadenectomy	Number of cases	15	1%	8	1%	4	0·9%	0	0%	1	2%	3	0·9%
	1 procedure †	14	93%	7	88%	3	75%	0	0%	1	100%	3	100%
	2 procedures †	1	7%	1	13%	1	25%	0	0%	0	0%	0	0%
Gynaecologic resection	Number of cases	17	2%	4	1%	3	0·7%	0	0%	1	2%	0	0%
	1-2 procedures †	17	100%	4	100%	3	100%	0	0%	1	100%	0	0%
Urologic resections	Number of cases	10	1%	4	1%	2	0·5%	1	2%	1	2%	0	0%
	1-2 procedures †	10	100%	4	100%	2	100%	1	100%	1	100%	0	0%
Subcutaneous or skin resections	Number of cases	10	1%	3	1%	1	0·2%	1	2%	1	2%	0	0%
	1-3 procedures †	10	100%	3	100%	1	100%	1	100%	1	100%	0	0%
Palliative surgery	Number cases	30	3%	18	3%	10	2%	3	5%	2	4%	3	7%

*** Other sites include intra-abdominal, distant bowel wall, kidney/ureter, gynaecologic, urologic, pleural, suprarenal, renal, pancreatic, thyroid, muscle and intravascular metastases.**
Data are n (%) unless otherwise specified. § Proportions of total number of first resections and/or ablations. ¶ Proportions of total number of second resections and/or ablations. # Proportions of total number of surgeries of primary. † Proportions of total number of resections and/or LAT procedures.
HIPEC= hypertermic intra-peritoneal chemotherapy.

RESULTS – SURGERY AND SYSTEMIC THERAPY FOR MULTIPLE METASTATIC SITES

Appendix Table 14. Metastatic sites during disease trajectory, surgery, local ablative therapy, and systemic therapy by metastatic site in patients with multisite metastases at baseline according to liver & extrahepatic, lung & extrapulmonary, peritoneal & extraperitoneal and other multisite metastases.

		All multisite		Liver & extrahepatic		Lung & extrapulmonary		Peritoneal. & extraperitoneal		Other multiple	
		500	100%	382	100%	264	100%	130	100%	346	100%
Metastatic sites during trajectory											
Metastatic sites	1			..	..	..	..	..	..	..	..
	2	163	33%	125	33%	91	34%	23	18%	83	24%
	3 to 9	337	67%	257	67%	173	66%	107	82%	263	76%
New metastatic sites											
Liver	Trajectory	403	81%	..	..	223	84%	83	64%	251	73%
Lung	Trajectory	326	65%	265	69%	..	..	57	44%	189	55%
Peritoneum	Trajectory	179	36%	113	30%	53	20%	..	..	131	38%
Lymph nodes	Trajectory	304	61%	222	58%	141	53%	70	54%	272	79%
Local relapse	Trajectory	72	14%	36	9%	19	7%	23	18%	67	19%
1-5 other sites	Trajectory	127	25%	70	18%	44	17%	21	16%	127	37%
Surgery and systemic therapy											
Resection status	Resectable & R0-1 resected	34	7%	18	5%	11	4%	12	9%	25	7%
	Resectable & R2 or LAT	16	3%	8	2%	1	0·4%	5	4%	12	3%
	Converted & R0-1 resected	14	3%	9	2%	10	4%	4	3%	11	3%
	Converted & R2 or LAT	26	5%	21	5%	15	6%	6	5%	17	5%
	Not resected	410	82%	326	85%	227	86%	103	79%	281	81%
First line therapy	Comb. CT & anti-EGFR	52	10%	169	44%	28	11%	9	7%	40	12%
	Comb. CT & anti-VEGF	267	53%	92	24%	146	55%	68	52%	186	54%
	Comb. CT (no biologic)	92	18%	51	13%	49	19%	27	21%	59	17%
	Single CT +/- anti-VEGF/-EGFR	76	15%	26	7%	34	13%	23	18%	52	15%
	No systemic therapy	13	3%	44	12%	7	3%	3	2%	9	3%
First resection §	Conversion (+ adjuvant)	37 (18)	41%	27 (12)	48%	18 (7)	49%	8 (5)	53%	12 (11)	36%
	Neoadjuvant (+ adjuvant)	24 (11)	27%	19 (9)	34%	15 (6)	41%	3 (2)	20%	13 (6)	39%
	Adjuvant	8	9%	1	2%	1	3%	4	27%	8	24%
	Only resection	21	23%	9	16%	3	8%	0	0%	0	0%
Second resection ¶	Conversion (+ adjuvant)	20 (9)	43%	13 (7)	46%	5	31%	5 (2)	42%	17 (8)	63%
	Neoadjuvant (+ adjuvant)	7 (5)	15%	5 (3)	18%	3	19%	3 (3)	25%	6 (5)	22%
	Adjuvant	8	17%	1	4%	3	19%	4	33%	4	15%
	Only resection	12	26%	9	32%	5	31%	0	0%	0	0%
Systemic therapy	Disease control intent	462	92%	354	93%	247	94%	119	92%	321	93%
	Only curative treatment	25	5%	15	4%	10	4%	8	6%	16	5%
	Best supportive care only	13	3%	13	3%	7	3%	3	2%	9	3%
Best response	CR/NED	20	4%	9	2%	5	2%	8	6%	5	1%
	PR	173	35%	197	52%	130	49%	52	40%	19	5%
	SD	150	30%	109	29%	87	33%	36	28%	169	49%
	PD	77	15%	61	16%	38	14%	28	22%	103	30%
	Not evaluated	6	1%	6	2%	4	2%	2	2%	50	14%
Primary surgery	Never operated	165	33%	152	40%	102	39%	33	25%	106	31%
	Upfront	297	59%	196	51%	143	54%	93	72%	217	63%
	During therapy	38	8%	34	9%	19	7%	4	3%	23	7%
Primary radicality #	R0	296	88%	208	90%	148	91%	77	79%	211	88%
	R1	21	6%	13	6%	9	6%	8	8%	16	7%
	R2	18	5%	9	4%	5	3%	12	12%	13	6%
Number resections & LAT	1	42	47%	26	46%	20	54%	11	41%	30	46%
	2	29	32%	17	30%	9	24%	10	37%	23	35%
	3 to 11	19	21%	13	23%	8	22%	6	22%	12	18%
Resection radicality †	R0	65	72%	48	86%	30	81%	11	41%	42	65%
	R1	14	16%	4	7%	4	11%	8	30%	13	20%
	R2	11	12%	4	7%	3	8%	8	30%	10	15%
Resections by metastatic site											
Liver resection and/or LAT	Number of cases	53	11%	50	13%	30	11%	5	4%	28	8%
	1 procedure †	42	79%	40	80%	27	90%	3	60%	18	64%
	2 procedures †	8	15%	8	16%	3	10%	1	20%	7	25%
	3 to 5 procedures †	3	6%	2	4%	0	0%	1	20%	3	11%
Lung resection and/or LAT	Number of cases	22	4%	15	4%	19	7%	5	4%	10	3%
	1 procedure †	15	68%	9	60%	12	63%	4	80%	7	70%
	2 to 8 procedures †	7	32%	6	40%	7	37%	1	20%	3	30%
Cytoreductive sugery +/- HIPEC	Number of cases	28	6%	6	2%	4	2%	23	18%	27	8%
	1 procedure †	25	89%	6	100%	4	100%	20	87%	24	89%
	2 procedures †	3	11%	0	0%	0	0%	3	13%	3	11%
Local relapse surgery	Number of cases	29	6%	12	3%	2	0·8%	14	11%	29	8%
	1 procedure †	25	86%	11	92%	2	100%	14	100%	25	86%
	2 procedures †	4	14%	1	8%	0	0%	0	0%	4	14%
Distant lymphadenectomy	Number of cases	7	1%	4	1%	3	1%	2	2%	5	1%
	1 procedure †	7	100%	4	100%	3	100%	2	100%	5	100%
	2 procedures †	0	0%	0	0%	0	0%	0	0%	0	0%
Gynecologic resection	Number of cases	13	3%	6	2%	2	0·8%	8	6%	13	4%
	1-2 procedures †	13	100%	6	100%	2	100%	8	100%	13	100%
Urologic resections	Number of cases	6	1%	4	1%	0	0%	1	0·8%	6	2%
	1-2 procedures †	6	100%	4	100%	0	0%	1	100%	6	100%
Subcutaneous or skin resections	Number of cases	7	1%	3	0·8%	0	0%	3	2%	5	1%
	1 to 3 procedures †	7	100%	3	100%	0	0%	3	100%	5	100%
Palliative surgery	Number of cases	12	2%	8	2%	1	0·4%	5	4%	10	3%

*** Other sites include intra-abdominal, distant bowel wall, kidney/ureter, gynaecologic, urologic, pleural, suprarenal, renal, pancreatic, thyroid, muscle and intravascular metastases.**
Patients are recorded recorded in multiple categories. Data are n (%) unless otherwise specified. § Proportions of total number of first resections and/or ablations. ¶ Proportions of total number of second resections and/or ablations. # Proportions of total number of surgeries of primary. † Proportions of total number of resections and/or LAT procedures.
HIPEC= hyperthermic intra-peritoneal chemotherapy. LAT= local ablative therapy. Perit. = peritoneal

RESULTS – SAFETY OF RESECTION AND/OR LAT

Appendix Table 15. Morbidity at 8 weeks and 30-day mortality from resection and/or local ablative therapy (LAT)

		Total	
		660	100%
Any complication	No	445	67%
	Yes	215	33%
Postoperative bleeding	No	651	99%
	Yes	9	1%
Wound complication	No	605	92%
	Yes	55	8%
Postoperative infection	No	523	79%
	Confirmed	105	16%
	Suspected	32	5%
Other complication	No	600	91%
	Yes	60	9%
30-day mortality after each metastasectomy *	No	658	100%
	Yes	2	0·3%

*** 2 of 399 (0·5%) died of massive bleeding, one at liver resection and the second during lymphadenectomy.**

RESULTS – SAFETY OF FIRST-LINE SYSTEMIC THERAPY

Appendix Table 16. Worst grade of most common (>5%) adverse event groups associated with chemotherapy, with or without biologics*

		All systemic		R0-1 resection		R2 or LAT		"Systemic therapy alone"	
		1060	100 %	324	100 %	72	100 %	664	100 %
Worst toxicity	Gr 3-4	681	64 %	192	59 %	49	68 %	440	66 %
Nausea or vomiting	Gr 3-4	64	6 %	15	5 %	5	7 %	44	7 %
Diarrhoea	Gr 3-4	84	8 %	16	5 %	6	8 %	62	9 %
Skin§	Gr 3-4	48	5 %	12	4 %	3	4 %	33	5 %
Infections	Gr 3-4 (5)	285 (5)	27 %	61	19 %	21	29 %	203 (5)	31 %
Thromboembolic event	Gr 3-4 (5)	79 (1)	8 %	20	6 %	5	7 %	54 (1)	8 %
Leukocytopenia	Gr 3-4	72	7 %	20	6 %	2	3 %	50	8 %
Transaminase elevated	Gr 3-4	62	6 %	37	11 %	9	13 %	16	2 %

***Patients were divided into three groups: curative resection (R0-1), R2 resection of metastases or primary, Local Ablative Therapy (LAT) or not all tumour sites resected curatively (R2/LAT); "systemic therapy alone" group. Excluded are 23 patients with best supportive care and 3 patients with metastasectomy without systemic therapy.**
§ mostly palmoplantar erythrodysesthesia, acneiform rash, and paronychia.
Additional grade 5 toxicities: cardiac events (n=1 in R2/LAT and n=1 in "systemic therapy alone" group), and allergic reaction (n=1 in "systemic therapy alone" group).

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STUDY PROTOCOL

RAXO trial

A population-based prospective study to evaluate clinical behaviour, resectability and survival in metastatic colorectal cancer patients in Finland

Date of Protocol: 29.8.2011_FINAL
3.12.2015_Version_2.0
30.10.2016_Version_3.1
07.05.2017_Version_3.2

SUMMARY

Protocol title:	A population-based prospective study to evaluate clinical behaviour, resectability and survival in 1st line metastatic colorectal cancer (CRC) patients in Finland The RAXO trial
Protocol version:	07.05.2017_Version_3.2
Principal Investigator	Pia Österlund; MD, PhD; associate professor Helena Isoniemi; MD, PhD; professor
Study Sponsor	Academic sponsorship
EudraCT number	2011-003158-24
Project phase	1) Prospective clinical trial and 2) Data collection trial
Indication	Metastatic cancer of the colon or rectum
Objectives	Primary objective: • To assess clinical behaviour of metastatic colorectal cancer and overall resectability, postoperative morbidity and outcomes after resection Secondary objectives: • To assess treatments for mCRC • To assess efficacy of chemotherapy and targeted drugs with overall response rates (ORR), failure free survival (FFS), progression free survival (PFS)· and overall survival (OS) • To radiologically assess tumour density and morphology· and assess alternative radiologic response evaluation in comparison with RECIST response criteria • To evaluate whole blood· plasma· serum and tumour block biomarkers and DNA polymorphisms that may predict drug effects· resectability and clinical behaviour of the tumour in the prospective cohort. • Biomarker evaluation from diagnostic samples, mainly tumour blocks, in the retrospective data collection trial in order to verify diagnosis and predictive & prognostic markers (from prospective clinical trial) in a big population based series. • Quality of life and health related qualify of life, Cost-utility, QALY and cost-benefit assessment in the subpopulation of 100-200 patients.
Planned sample size	In total 1000 patients will be recruited in the clinical trial part of the study. Recruitment to the clinical trial will be between November 2011 and December 2018. Population based assessment in the data collection trial during the time period of recruitment to the clinical trial.
No. of centres	All hospitals treating colorectal cancer in Finland (appr. 20)

Selection criteria	**Inclusion criteria** 1. Patients with histologically confirmed CRC, who are scheduled to start or are getting first line chemotherapy for metastatic disease 2. Age ≥ 18 3. Metastatic disease (including locally advanced disease not amenable with surgery and/or (chemo)radiotherapy) 4. Signed written informed consent according to ICH/GCP and the local regulations (approved by the Independent Ethics Committee [IEC]) will be obtained prior to study 5. No informed consent will be obtained from patients participating in the data collection study obtaining data from hospital charts. No blood sampling, nor contacting of patients will be performed.
Resectability	Patients will be centrally assessed for resectability at baseline and thereafter for a maximum of 3 times (mainly for liver and lung metastasectomies) every 8-12 weeks.
Standard medical treatment	In each clinic standard medical treatment will be administered until disease progression, unless unacceptable drugtoxicity is experienced or until resectability is achieved. At least 3 months of the same chemotherapy treatment should be given at the physicians discretion following metastasectomy.
Study procedures	**Informed consent:** Separate written informed consent must be obtained before the patient participates in the prospective resectability evaluation study or in the blood sampling for biomarkers.
	Screening: Baseline screening includes following assessments: • According to local standard practice: - Demographic data, medical history, cancer/treatment history and concomitant medications - ECOG performance status and physical examination - Tumour assessments i.e. whole body CT (in combination with MRI and PET according to subprotocols or local standards) before treatment starts - Central assessment of resectability initiated - Whole blood for DNA, plasma and serum at the baseline - Tumour blocks collected

	The following data will be collected during treatment: • According to local standard practice: - Spontaneous adverse event reporting according to local regulations, without data collection for the study purposes - Monitoring of concomitant diseases, treatments, medications and compliance to drugs - Physical examination - Assessments of tumour response using whole-body CT (or MRI/PET according to subprotocols) - Confirmation of overall response • Resectability will be assessed centrally after baseline for a maximum of 3 times every 8-12 weeks during the treatment • Plasma and serum will be collected at the same time as tumour assessment and after last chemotherapy cycle
	The following data will be collected during follow-up: • According to local standard practice: - Assessments of tumour response - Subsequent treatments - Spontaneous adverse event reporting, without data collection for the study purposes
Data collection procedures	In addition to the 1000 consenting patients participating in the clinical study; the data collection cohort will gather population based information from the cancer registry and from hospital charts for metastatic colorectal cancer patients. Similar inclusion criteria will be used, but no blood sampling or patient contacting will be performed. Inclusion period will be identical with the clinical study.
Statistical considerations	The primary objective is to assess clinical behaviour of mCRC and the overall resectability rate, postoperative morbidity and outcomes after resection, compared between chemotherapy regimens. The secondary objectives, i.e. treatments, RR, FFS, PFS, and OS will also be assessed overall and compared between chemotherapy regimens. The planned size of 1000 patients (the expected Finnish yearly patient population) is considered to provide very sufficient precision for the clinical behaviour of mCRC and for assessment of overall resectability rate. Based on historical data, among 20% (200) of the Finnish yearly population are expected to have liver only disease with a resectability rate of 20% (40). With this sample size the width of the 95% confidence interval of the resectability rate will be approximately ± 5.5%.
Analysis plan	The primary analyses will be based on the intent-to treat population, which will include all eligible patients.

	A 95% confidence interval will be calculated for the overall resectability rate. Comparisons between chemotherapy regimens will be done using a chi-square test as well as with a logistic regression model will be used, if feasible. Resection outcome and postoperative morbidity will be presented at least by descriptive statistics. Survival outcomes, i.e. FFS, PFS, and OS will be estimated for the overall population and for all chemotherapy regimens using the Kaplan-Meier approach. In addition, these parameters will be analyzed using the Cox-proportional hazard model. The RR will be analyzed using chi-square test. Radiological assessments with tumour density and morphology will be analyzed using analysis of covariance ANCOVA, with the RECIST response criteria as a covariate.
Duration of the study	It is expected that the first patient is enrolled in 2011 and the enrolment will be completed during 2018. Patients will be followed-up for 10 years after inclusion, until 2025.

STUDY RELATED ASSESSMENTS

Schedule	Screening / Baseline	Treatment[1] Every 8-12 weeks	Post-treatment follow up
Eligibility assessment	X		
Informed consent	X		
Demographic data	X[1]		
Medical & cancer treatment history. Concomitant medications.	X[1]	X[1]	X[1]
Tumour assessment (preferably whole body CT)	X	X[2][3]	X[4]
Central assessment of resectability	X	X[3]	
ECOG performance status	X[1]	X[1]	X[1]
Physical examination	X[1]	X[1]	X[1]
Research blood samples[5]	X	X	X
Follow up on disease progression, anticancer therapies and survival			X

[1] According to local standard practice
[2] Response verification recommended after 4-9 weeks
[3] Central assessment of resectability will be performed every 8-12 weeks for a maximum of three times
[4] If no progressive disease seen when coming off study
[5]Whole blood (10 ml EDTA-tube) for DNA at the baseline. Plasma and serum, in 30+20ml EDTA/heparin/citrate-tube and 20ml serum/gel/vacutainer-tube), will be collected at the baseline and thereafter every 8-12 weeks (at the same time as tumour assessment) and after last chemotherapy cycle

TABLE OF CONTENT

BACKGROUND

1.1. DISEASE BACKGROUND

Colorectal cancer is one of the most frequent malignancies, second to breast cancer in women and third to prostate and lung cancer in men [1,2]. The prognosis for the individual patient is dependent upon the extent of the disease. The 5-year survival rate is over 60% in individuals with resectable cancer, but less than 5% in individuals with distant metastatic disease [2-5].

The clinical course of mCRC is of special interest. Sites of metastases primarily is of crucial value whether they are or going to be operable (typically lung or liver metastases) or not (eg. bone metastases). Ten per cent of patients with metastases confined to the liver are considered initially resectable and another 10-15% may be rendered resectable with efficient treatment, but the corresponding figures for lung metastasectomies are unknown. To the best of our knowledge this has not been assessed population based with central resectability evaluation. Co-morbidities and patient/caregiver preference in choice of active treatment and best supportive care has not been thoroughly evaluated in population based manner in mCRC.

1.2. CHEMOTHERAPEUTIC AGENTS FOR COLORECTAL CANCER

Most metastatic colorectal cancer patients are treated with chemotherapy with palliative intent. In locally advanced and distant metastatic disease 5-fluorouracil (5-FU) based chemotherapy improves quality of life and survival compared with best supportive care alone [2,3,6]. Intravenous 5-FU is most efficient when combined with folinic acid (leucovorin, LV) and may be dosed as repeated bolus injections or short/long infusions [7]. Capecitabine (Xeloda™) is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour tissue through exploitation of high intratumoural concentrations of thymidine phosphorylase [8].

Oxaliplatin is a platinum derivative in which the platinum atom is complexed with a 1,2 diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group [9]. Oxaliplatin has been widely studied and is active as monotherapy in front-line or subsequent therapy settings in patients with mCRC [10-13].

Irinotecan is a semi-synthetic derivative of camptothecin and belong to the class of topoisomerase I inhibitors. The efficacy of irinotecan given as a single agent has been assessed in first and second line settings [14, 15].

1.2.1. COMBINATION CHEMOTHERAPY

Phase III trial results showed in 2000 the superiority of irinotecan or oxaliplatin as first-line treatment in combination with 5-FU/LV, compared to 5-FU/LV therapy alone [16-18]. Thus combination chemotherapy became the standard of care and new combination chemotherapy regimens have been explored.

Irinotecan in combination with both bolus and infusional 5-FU/LV has been shown to improve efficacy compared with 5-FU/LV alone in MCRC [8-9]. Also the combination of capecitabine plus irinotecan every 3 weeks (XELIRI regimen) has shown feasible safety and comparable efficacy [19, 20].

Oxaliplatin in combination with bolus and infusional 5-FU/LV has shown improved response rates and progression free as well as overall survival [10]. Oxaliplatin combinations has thus subsequently been evaluated also in combination with chronomodulated 5-FU and oral prodrugs. Capecitabine combinations (XELOX) has shown comparable efficacy and tolerability as infusional 5-FU based chemotherapy [19-22].

The triple combination of irinotecan, oxaliplatin and 5-fluoruracil has been evaluated in 2 randomized studies. In the Falcone study, the triple combination had superior efficacy compared with the FOLFIRI arm. Interestingly a high resection rate was seen in the Falcone study; R0 secondary resection rate was 15 vs. 6% in total population and 36 vs. 12% in the liver only metastases population [23]. In the Souglakos study, no significant benefit for the triple combination was seen [24]. This triple combination has though been considered too toxic in routine clinical care and leaves few options for further lines of chemotherapy. Modern combinations with targeted treatments (i.e. biologics) such as bevacizumab, cetuximab and panitumumab maybe too toxic in conjunction with triple chemotherapy.

1.3. BIOLOGICAL THERAPIES 1ST LINE COLORECTAL CANCER

Bevacizumab (Avastin™) is a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF). VEGF-A which is a ligand with a central role in signalling pathways controlling tumour blood vessel development and survival [25-28]. Several large trials have demonstrated that bevacizumab improves the efficacy of fluoropyrimidine-based chemotherapy in previously untreated patients with metastatic CRC [29-30,22] improving significantly overall survival, progression-free survival, response rate, and response duration. In addition, safety and efficacy of first-line bevacizumab combined with various chemotherapies in patients with metastatic CRC have been demonstrated in phase IV studies [31-33].

Cetuximab (Erbitux™) and panitumumab (Vectibix™) are monoclonal antibodies against the epidermal growth factor receptor (EGFR) [34-35]. The efficacy of monoclonal antibodies against EGFR is limited to KRAS wild type tumours [36-37]. Both drugs first showed efficacy in later lines of therapy both as monotherapy [38-39] and in combination with irinotecan [40]. Recently also in first and second line settings [41-42].

Cetuximab has shown superior efficacy and resectability in first line in combination with irinotecan and 5-FU/LV (FOLFIRI) [43]. Oxaliplatin and 5-FU based combinations to cetuximab have shown conflicting results and need further evaluation [44]. The biological doublet with Cetuximab and Bevacizumab showed inferiority [45].

Panitumumab as first line therapy has shown superior efficacy and resectability in combination with oxaliplatin and 5-FU/LV (FOLFOX) [46]. The biology doublet of panitumumab and bevacizumab in first line showed inferiority especially in combination with FOLFOX and no benefit in patients with FOLFIRI [47].

1.4. RESECTION OF LIVER METASTASIS

The liver is the most common site of haematogenous metastasis from gastrointestinal malignancies due to portal venous blood flow from the intestine.

In the past patients with liver metastasis were often deemed inoperable. As a result of improved techniques, major hepatic resection is nowadays performed with acceptable morbidity and low perioperative mortality, under 5% in major hepatobiliary centres [48]. For patients with mCRC liver resection is the only available treatment with an option of long-term survival and also prolonged disease-free survival. Several reports have established the efficacy of surgical resection in selected patients with 5-year survival rates ranging from 37 to 71% [49-52].

However curative operation can be performed only in a small minority of all patients with colorectal metastases confined to the liver and no survival benefit is obtained from incomplete resection [54]. Today the amount of patients with curative intent surgery can be increased after down staging initially unresectable lesions by chemotherapy [53].

Neoadjuvant chemotherapy for two to six months with regular re-evaluation for resectability has been advocated as the optimal strategy to maximize respectability [48,54]. Long oxaliplatin exposure has been linked with blue liver causing increased bleeding in liver resections [55] and long irinotecan based chemotherapy causes steatohepatosis, which may increase morbidity in conjunction with liver resections [56]. Recently published data suggest that bevacizumab may be preventing liver injury from chemotherapy in conjunction with neoadjuvant chemotherapy [57]. Thus routine re-evaluation for liver resectability is done for a maximum of three times during first line chemotherapy.

There is currently one report of a randomized controlled trial evaluating liver resection alone with neoadjuvant and adjuvant therapy combined with liver resection, showing an advantage to the outcome of hepatic resection [53]. Some recent reports and reviews propose an advantage using adjuvant chemotherapy after liver resection [48,54,58,59]. With the development of better chemotherapeutic agents, which may eradicate residual microscopic tumour cell deposits in the liver and elsewhere, partial hepatectomy to remove focal macroscopically observed metastases is likely to be more common and more effective.

1.5. RESECTION OF LUNG METASTASES

Lung is the second most common site of metastases of CRC. CRC is recognized to be the most common primary histology for patients with potentially resectable pulmonary metastases. However the incidence of isolated lung metastases without associated metastases for CRC patients is low (<10%).

No randomized controlled trials exist to date to analyze the outcomes of patients who underwent resection of pulmonary metastases secondary to colorectal cancer. However, several centres have published results from case series, showing 5-year survival of 29-56% and a median survival from 47-74 months [60-63].

Several clinical patient series describe criteria for pulmonary metastasectomy. However, no prospective randomized trials for pulmonary metastasectomy makes it difficult to summarize and evaluate the effectiveness of this operation

There has been data reported that indicates that patients with history of previous liver metastases have a higher risk of tumour recurrence and a decreased survival in comparison with patients who underwent surgery for lung-only CRC metastases [64]. On the other hand, there are also reports concluding that resectable or resected liver metastases might not impact the survival after pulmonary metastasectomy [65].

Different reviews of studies analyzing prognostic factors differ. Thus, there are reviews reporting that number and location of metastases, disease-free interval between resection primary colorectal cancer and detection of pulmonary metastases, pre-resection CEA level, thoracic lymph-node metastasis, level of prethoracotomy serum-carcinoembryonic antigen, age, gender, site and stage are prognostic factors for improved survival rates [65-66].

Still most reviews of studies analyzing prognostic factors such as number of nodules, size of the dominant nodule, disease-free interval, or use of chemotherapy to mention just a few, found no prognostic significance [66-67].

Surgical resection is the primary treatment modality for pulmonary metastases in colorectal cancers in patients who meet the criteria for potentially curative operation. United Kingdom National Institute for Clinical Excellence guidance makes a similar recommendation. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology precondition for potentially curative operation as follows:

- the metastases seem to be technically resectable,
- the general and functional risks are tolerable,
- the primary tumour is controlled, and
- no extrathoracic lesions are detected (with the exception of hepatic lesions in which it is possible to completely remove both hepatic and pulmonary metastases).

The role of chemotherapy in the treatment of patients with metastatic colorectal cancer is evolving. Although in most studies chemotherapy has been a standard therapy for metastatic colorectal cancer, the impact of neoadjuvant and adjuvant chemotherapy in the context with pulmonary metastasectomy on long-term survival had not been sufficiently addressed [66].

The integration of systemic targeted therapy should be considered in decision making regarding candidacy and timing for surgery.

1.6. ASSESSMENT OF RESECTABILITYY OF LIVER AND LUNG METASTASES

Patients will be centrally assessed for resectability at baseline and after 8-12 weeks during chemotherapy maximally three times. Treatment with bevacizumab should be stopped at least 4 to 6 weeks before surgical intervention in patients who are to be referred for resection. During this time the patient may receive one or more chemotherapy doses, as clinically appropriate. Chemotherapy and biologicals may be restarted 4 weeks after surgery and bevacizumab when wound healing is complete

1.7. RADIOLOGY ASSESSMENT

Radiological assessment with whole-body CT two-monthly has been standard. WHO criteria for response were defined in 1982 and replaced by RECIST criteria in 2000. These RECIST criteria have been revised recently [68] but still leaves open the question of how to evaluate the efficacy of chemotherapy, especially in combination with biologicals, radiologically. In GIST for example metabolic activity assessed with PET was found much more reliable [69-74]. So far PET has not shown significant advantage over whole-body CT in response evaluation [75] and the role of PET needs to be established.

MRI of liver is another question not fully answered. Over the past decade liver MRI has been recommended when liver resection has been evaluated but the development of the CT technology has made the role of

MRI debatable. Recently reports of altered density and morphology of for example liver metastases after chemotherapy and biologicals has been seen on radiology [76].

This study aims to explore improved radiological evaluation methods in mCRC compared with RECIST CTs.

1.8. RATIONALE FOR HEALTH-RELATED QUALITY OF LIFE AND BIOMARKER ASSESSMENTS

The study will be performed in order to analyse the clinical behaviour and treatments for mCRC population based. Central assessment of resectability will also provide a more reliable estimate of the respectability rate in Finnish metastatic CRC patients. The rationale for this study is to evaluate which treatment modalities result in higher resectability rates as well as a longer progression free survival and overall survival. Improved radiologic assessment methods and prognostic factors will also be evaluated.

Health related quality of life (HR QoL) issues and cost-utility, cost-benefit and quality adjusted life year gain (QALY) is becoming increasingly important with prolonged survival in this patient population due to improving treatment alternatives. Therefore QoL questionnaires EORTC QLQ-C30 and CR29· EQ5 and 15D will be administered to new patients to be included in the prospective clinical study· estimated 150-200 patients· which is a fair subgroup for these analysis.

Biomarkers and personalized medicine is becoming increasingly important in treatment of metastatic colorectal cancer. Prognostic markers as BRAF and predictive markers as KRAS and NRAS are used in clinical practise but several other markers are to be validated.

The inclusion criteria for the RAXO study are patients with first line treatment and therefore a significant proportion of metastatic patients with aggressive disease, old age and comorbidities are not consented and thus participate in the data collection trial. Many discrepancies for example in BRAF mutation frequency have been noted among clinical study patients with a frequency of 4 to 8% and over 20% in more population-based series (as the data collection trial) (Sörbye et al, 2015, Annika Ålgars personal communication 7.9.2016). Systemic consenting of patients to the prospective clinical study was not performed in the early days of the inclusion period due to logistic reasons.

The prospective trial will consist of slightly selective patients and therefore the diagnostic samples of the data collection trial identified via the cancer registry, the hospital and National institute of health and welfare (THL) registries are used to verify diagnosis and predictive and prognostic markers population based.

Samples up til 1st September 2013 have been transferred or are due to be transferred to the Biobanks, they are used with permission by the Biobanks. Samples from 1st September 2013 are under the biobank laws of Finland but very few patients have been given the opportunity to consent especially during the first years. Therefore they cannot be used under this permission and due to the nature of metastatic disease the majority of patients cannot be consented as of now. The majority of cases before the biobank era are also deceased and cannot consent. Cases that have declined participation into the RAXO-study will not be used in the biomarker population.

The diagnostic samples, mainly tumour tissue from data collection trial, are clinically relevant when they provide population-based information about the nature of the disease and treatment options with valuable prognostic and predictive markers benefitting metastatic colorectal patients in the future. Permission for use of these diagnostic samples are requested from VALVIRA and the ethical board.

STUDY OBJECTIVES

1.9. PRIMARY OBJECTIVES

- To assess clinical behaviour of metastatic colorectal cancer and overall resectability, postoperative morbidity and outcomes after resection

1.10. SECONDARY OBJECTIVES

- To assess treatments for mCRC

- To assess efficacy of chemotherapy and targeted drugs wtih overall response rates (ORR), failure free survival (FFS), progression free survival (PFS) and overall survival (OS)
- To radiologically assess tumour density and morphology, and assess alternative radiologic response evaluation in comparison with RECIST response criteria
- To evalute whole blood, plasma, serum and tumour block biomarkers and DNA polymorphisms that may predict drug effects, resectability and clinical behaviour of the tumour
- Biomarker evaluation from diagnostic samples, mainly tumour blocks, in the data collection trial in order to verify diagnosis and predictive & prognostic markers (from prospective clinical cohort) in a big population based series.
- Quality of life and health related qualify of life, Cost-utility, QALY and cost-benefit assessment in the subpopulation of 100-200 patients.

STUDY DURATION

It is expected that the first patient is enrolled in 2011 and the enrolment will be completed during 2018. Patients will be followed-up for 10 years after inclusion, until 2025.

SELECTION CRITERIA

1.11. INCLUSION CRITERIA

1. Patients with histologically confirmed CRC, who are scheduled to start or are getting first line chemotherapy for metastatic disease
2. Age $\geq$ 18
3. Metastatic disease (including locally advanced disease not amenable with surgery and/or (chemo)radiotherapy)
4. Signed written informed consent according to ICH/GCP and the local regulations (approved by the Independent Ethics Committee) will be obtained prior to study
5. No informed consent will be obtained from patients participating in the data collection study obtaining data from hospital charts without blood sampling and contacting of patients

STUDY DESIGN

1.12. DESIGN

1) Prospective clinical trial and 2) data collection trial.

1.13. STUDY PROCEDURES PER VISIT

Please refer to the Assessment flow chart (Table 1) for an overview.

1.13.1. SCREENING AND BASELINE

Signed informed consent has to be obtained from all patients prior to blood sampling and central assessment of resectability. The investigator will register the consenting patient at the co-ordinating centre. The following data will be collected and recorded:

Baseline/screening includes following assessments:

- According to local standard practice:
- Demographic data, medical history, cancer/treatment history and concomitant medications
- ECOG performance status and physical examination

- Tumour assessments i.e. whole body CT (in combination with MRI and PET according to subprotocols or local standards) before treatment starts
- Central assessment of resectability initiated
- Whole blood for DNA, plasma and serum at the baseline
- Tumour blocks collected

1.13.2. TREATMENT PHASE

Patients will receive the local standard of care treatment and according to standard practice they will have scheduled visits in conjunction with treatment infusions.

The following data will be collected during treatment:

- According to local standard practice:
- Spontaneous adverse event reporting according to local regulations, without data collection for the study purposes
- Monitoring of concomitant diseases, treatments, medications and compliance to drugs
- Physical examination
- Assessments of tumour response using whole-body CT (or MRI/PET according to subprotocols)
- Confirmation of overall response
- Resectability will be assessed centrally after baseline for a maximum of 3 times every 8-12 weeks during the treatment
- Plasma and serum will be collected at the same time as tumour assessment and after the last chemotherapy cycle

1.13.3. POST-TREATMENT FOLLOW UP

First line cancer treatment will be terminated when disease progression is identified or if toxicity is experienced that in the view of the patient or doctor is unacceptable.

The following data will be collected during follow-up:

- According to local standard practice:
- Assessments of tumour response
- Subsequent treatments
- Spontaneous adverse event reporting, without data collection for the study purposes

1.13.4. BIOLOGICAL SAMPLES

Blood samples for biomarker analyses will be collected from those patients who give the consent for the biomarker study. Blood samples will be collected at the baseline, at efficacy assessments during the treatment phase and at the final visit.

Sample collection will include whole blood (10 ml EDTA-tube) for DNA at the baseline. Plasma and serum, 18ml and 12 ml each, (in 30ml EDTA/heparin/citrate-tube and 20ml serum/gel/vacutainer-tube), will be collected at the baseline and thereafter every 8-12 weeks (at the same time as tumour assessment) and after last chemotherapy cycle

Serum and plasma samples are collected for protein analyses (blood collected into an tube as defined in Table 1) and blood samples for DNA extraction in order to measure DNA polymorphism. The set of plasma biomarkers will be analyzed including but not limited to: biomarkers that predict the clinical behaviour of the tumour, angiogenesis, resectability and regeneration biomarkers.

Baseline sample:
- both plasma and serum samples and blood samples for DNA extraction will be collected as defined in Table 1.

Every 8-12 weeks during the treatment phase in conjunction with efficacy assessment:
- serum and plasma samples for protein analyses will be collected as defined in Table 1.

The last visit:
- serum and plasma samples for protein analyses will be collected as defined in Table 1.

1.13.5. TERMINATION OF STUDY

The survival status of each patient and subsequent treatments should be assessed at the end of 1st line chemotherapy, at three months intervals according to the standard visit schedule, and at the end of follow-up i.e. death of the patient, withdrawal of consent or termination of the study.

STUDY MEDICATION

1.14. STANDARD MEDICAL TREATMENT FOR MCRC

The clinic's standard medical treatment will be administered until disease progression, unless unacceptable toxicity is experienced or until resectability is achieved. Stop and go strategy is used according to local standard. Progression on first line treatment is defined as when resistance to reintroduced drugs is verified.

1.14.1. STANDARD MEDICAL TREATMENT IN CONNECTION WITH SURGERY

Patients who are to be referred for liver or lung resection will receive scheduled treatment up to 3 weeks before surgery. No bevacizumab should be given within 4-8 weeks before (thus bevacizumab is often omitted from the last cycle) and 4 weeks after surgery. Following metastasectomy at least 3 months of the same chemotherapy treatment should be given at the physicians discretion.

1.15. TREATMENT DURATION

Standard medical cancer treatment will be administered until disease progression is identified or if toxicity is experienced that in the view of the patient or doctor is unacceptable.

1.16. CONCOMITANT TREATMENT & THERAPY

1.16.1. OTHER MEDICATION

Any concomitant therapy is at the clinician's discretion and should be recorded.

1.16.2. RADIATION THERAPY

Should the patient need to undergo radiation therapy the procedure will be recorded.

PREMATURE WITHDRAWAL

1.17. WITHDRAWAL FROM STANDARD MEDICAL TREATMENT

All patients are allowed to withdraw from the study at any time and for whatever reason without affecting their right to an appropriate follow-up treatment.

WARNINGS AND PRECAUTIONS OF MEDICAL TREATMENT

For warnings and precautions concerning any of the standard medical treatments for colorectal cancer the reference document is the Summary of Product Characteristics.

SAFETY PARAMETERS

Safety variables according to local clinical practice will be monitored according to local standards but will not be collected for study purposes:

- Adverse events (inclusive serious adverse events)
- Vital signs
- Laboratory tests

SERIOUS ADVERSE EVENT REPORTING

The SAE reporting and annual safety reporting is the responsibility of the sponsor (=investigators) and are done according to the local legislation.
Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria.

1) SUSARs
The sponsor submits SUSARs to Health authority (FIMEA).

2) SAEs
Any protocol defined Serious Adverse Events and pregnancy reports that occur during the course of the study or within 4 weeks following treatment discontinuation or completion will be collected by the sponsor periodically.
Excluded from the requirement of expedited reporting are all expected events· although serious (Grade 3 or 4)· that are more common as 1% according to SPCs (summary of product characteristics) adverse event chapter. SAEs excluded from the requirement of expedited reporting are collected to AE-pages in case report forms and summarized at the end of the study.

3) AEs
AEs are collected to AE-pages in case report forms and information of these non-serious adverse events is summarized at the end of study.
The definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and local legislation will be adhered to. Complete information can be found in www.ich.org and www.nam.fi.

~~The treating physician is responsible for safety reporting to the local health authority (Fimea) according to local regulations and spontaneous reporting requirements~~ http://www.fimea.fi/lait_ja_ohjeet/ohjeet~~. Adverse events are not recorded and collected for study purposes.~~

~~Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria.~~

STATISTICAL CONSIDERATIONS

1.18. SAMPLE SIZE CALCULATION

The planned size of 1000 patients (the expected Finnish yearly patient population) is considered to provide very sufficient precision for the clinical behaviour of mCRC and for assessment of overall resectability rate. Based on historical data, among 20% (200) of the Finnish yearly population are expected to have liver only disease with a resectability rate of 20% (40). With this sample size the width of the 95% confidence interval of the resectability rate will be approximately ± 5.5%.

1.19. ANALYSIS POPULATION

The primary analysis of resectability rate will be based on all eligible patients who had at least one central resectability evaluation performed. The Intention-to-treat (ITT) approach, i.e. all eligible patients, will be applied on other analyses in this population based study.

1.20. ANALYSIS PLAN

This is a summary of the planned statistical analyses. The statistical analysis will be described more in detail in a separate statistical analysis plan.

The primary objectives are the clinical behaviour of mCRC and the overall resectability rate, postoperative morbidity and outcomes after resection. Different chemotherapy regimens will also be compared with respect to these parameters. A 95% confidence interval will be calculated for these parametres. Comparisons between clinical factors and chemotherapy regimens will be done using a chi-square test as well as a logistic regression model. As the expected number of resections is quite low, resection outcome and postoperative morbidity will be summarized mainly by descriptive statistics. However, a 95% confidence intervals will be calculated for overall resection outcome and postoperative morbidity rates.

Survival outcomes, i.e. failure free survival, progression free survival (PFS), and overall survival will be estimated for the overall population and for all chemotherapy regimens using the Kaplan-Meier approach. In addition, the Cox-proportional hazard model will be used for comparison of chemotherapy regimens in the analysis of these parameters.

The response rate will be summarized overall and the differences between chemotherapy regimens will be analyzed using chi-square test.

Tumour density and morphology will be summarized and analyzed using analysis of covariance ANCOVA, with the RECIST response criteria as a covariate.

The demographic and baseline characteristics will be summarized with descriptive statistics.

SIGNATURE

I agree to perform the clinical study according to the protocol, international good clinical practice principles and regulatory authority requirements.

PRINCIPAL INVESTIGATORS:

DATE & PLACE SIGNATURE

_____ _____

Professor Helena Isoniemi

_____ Helsinki University Central Hospital, Dept. of Surgery

DATE & PLACE SIGNATURE

_____ _____

Associate professor Pia Österlund

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GLOSSARY AND DEFINITION OF TERMS USED

AE	Adverse event
ALAT	Alanine amino transferase
ASAT	Aspartate amino transferase
CA19-9	Cancer antigen 19-9
CEA	Carcinoembryonic antigen
CNS	Central nervous system
CPT-11	Irinotecan
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
DACH	1,2-diaminocyclohexane
DPD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal growth factor receptor
FOLFOX	Infusional 5-FU, leucovorin and oxaliplatin (biweekly)
FOLFIRI	Infusional 5-FU, leucovorin and irinotecan (biweekly)
5-FU	5-fluorouracil
GCP	Good Clinical Practice
Gr	Grade
HUCH	Helsinki University Central Hospital
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
LV	Leucovorin (folinic acid)
MRI	Magnetic resonance imaging
NCI	National Cancer Institute (of the United States of America)
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall survival
PFS	Progression free survival
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TTP	Time to tumor progression or death
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WHO PS	WHO or Zubrod performance status
XELOX	Capecitabine, oxaliplatin

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