

Prognosis of lung metastases in patients with metastatic colorectal cancer (mCRC): an ARCAD metabase analysis

Julie Henriques, Dewi Vernerey, Aimery de Gramont, Benoist Chibaudel, Eric Van Cutsem, Alfredo Falcone, Richard M. Goldberg, Qian Shi, Franck Bonnetain, Einat Shacham-Shmueli

Fondation Aide et Recherche en Cancérologie Digestive (ARCAD) Group

Background

- Most common sites of mCRC: liver, lung, peritoneum
- Lung metastases are mostly asymptomatic, seldom the direct cause of death
- 5-years OS after surgical resection of pulmonary metastases: 24-56% ^[1-2]
- Retrospective data confusing – some report better OS, other worse ^[3-4]

1. Pfannschmidt et al *Ann Thorac Surg.* 2007;84(1):324–38. 10.

2. Quiros et al *Semin Oncol* 2008;35:134-46.

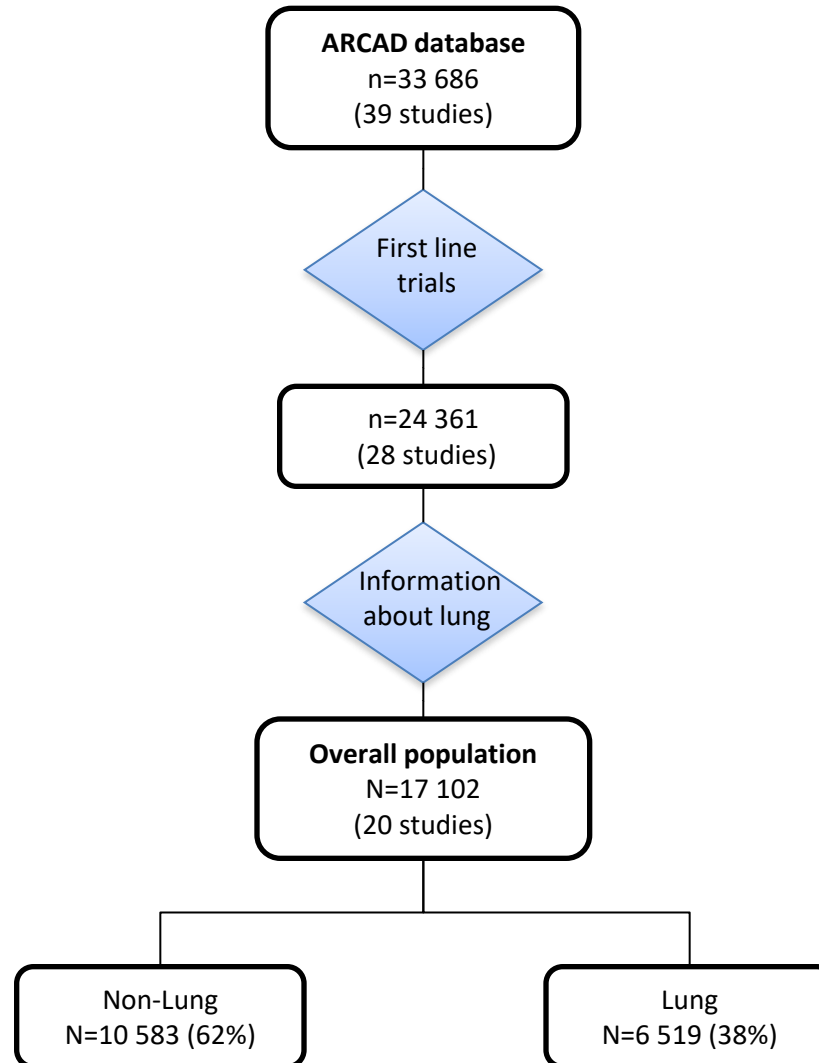
3. Lemmens et al *Int. J. Cancer* 2011, 128, 2717–2725

4. Neeff et al *J Gastrointest Surg.* 2009 Oct;13(10):1813-20

Aims

- Assess the prognostic value of lung metastases, as either single metastatic site or as part of multiple organ metastasis, for OS among mCRC patients

Population of analysis



Trials

- 20 first-line randomized trials
(11 of which included targeted regimens)

Study	Treatment	No. pts	% pts with Lung mets	First author & year publication
AVF2192g	5FU vs 5FU + BEV	208	50	Kabbinavar, 2005
AVF2107g	IFL vs IFL + BEV	921	48	Hurwitz, 2004
BICC-C	mIFL ± BEV vs FOLFIRI ± BEV vs cap + irinotecan	543	47	Fuchs, 2007
OPTIMOX2	mFOLFOX7 vs mFOLFOX7 (with complete stop)	201	44	André, 2007
COIN	FOLFOX vs FOLFOX + cet vs intermittent FOLFOX	2426	41	Maughan, 2011
HORG 99.30	FOLFOX + irinotecan vs FOLFIRI	282	41	Souglakos, 2006
N016966	FOLFOX4 vs FOLFOX4+BEV vs XELOX vs XELOX+BEV	2026	40	Saltz, 2008
CAIRO2	CAPOX + BEV vs CAPOX + BEV + cet	655	40	Tol, 2009
FOCUS2	5FU vs FOLFOX vs cap vs CAPOX	454	40	Seymour, 2011
HORIZON II	FOLFOX+ CAPOX + cediranib vs FOLFOX + CAPOX	1180	39	Hoff, 2012
AGITG (MAX)	Capecitabine vs cap + BEV vs cap + BEV + mitomycin	471	39	Tebbutt, 2010
CAIRO1	Cap vs cap+ irinotecan	646	37	Koopman, 2007
FOCUS	5FU vs 5FU + oxaliplatin vs 5FU + irinotecan	2071	36	Seymour, 2007
HORIZON III	FOLFOX + cediranib vs FOLFOX + BEV	1743	36	Schmoll, 2012
FIRE II (CIOX)	XELOX + cet vs cap + irinotecan + cet	177	36	Moosmann, 2011
TRIBE	FOLFIRI + BEV vs FOLFOXIRI + BEV	508	32	Cremolini, 2015
N9741	IFL vs FOLFOX vs irinotecan + oxaliplatin	1398	31	Goldberg, 2004
03-TTD-01	FUOX vs XELOX	338	31	Díaz-Rubio, 2007
GONO	FOLFOX + irinotecan vs FOLFIRI	242	30	Falcone, 2007
OPTIMOX1	FOLFOX4 vs FOLFOX7 (maintenance)	612	27	Tournigand, 2006

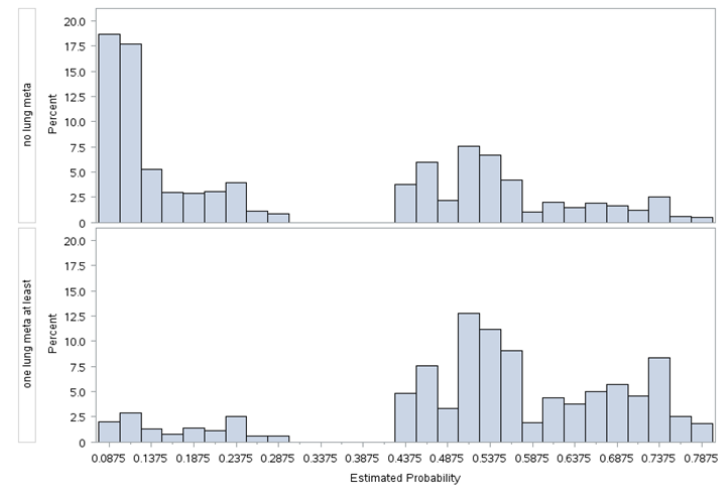
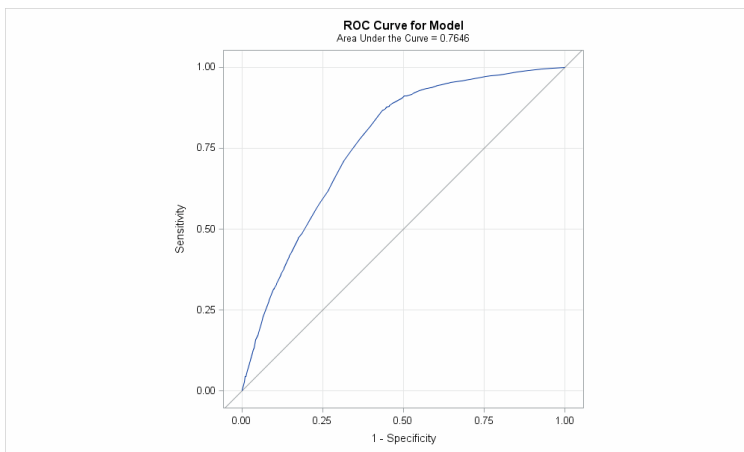
Patients characteristics

characteristics	Overall population (N=17102)		Population with lung metastasis (N=6519)		Population without lung metastasis (N=10583)		pvalue
	N		N		N		
Sexe	17091		6517		10574		0,7986
Male		10556 (61,76)		4033 (61,88)		6523 (61,69)	
Female		6535 (38,24)		2484 (38,12)		4051 (38,31)	
Age	17097		6516		10581		<0,0001
Median		63		63		62	
Q1-Q3		55-69		56-70		54-69	
BMI	15600		6037		9563		<0,0001
Median		25,36		25,7		25,15	
Q1-Q3		22,72-28,57		23,06-28,95		22,49-28,34	
ECOG PS	16878		6459		10419		0,2103
0		8925 (52,88)		3376 (52,27)		5549 (53,26)	
≥1		7953 (47,12)		3083 (47,73)		4870 (46,74)	
Tumor location	11587		4566		7021		<0,0001
Colon		8024 (69,25)		2766 (60,58)		5258 (74,89)	
Rectum		3378 (29,15)		1730 (37,89)		1648 (23,47)	
Colon +rectum		185 (1,60)		70 (1,53)		115 (1,64)	
No. of metastatic site	17102		6519		10583		<0,0001
1		7354 (43,00)		955 (14,65)		6399 (60,46)	
≥2		9748 (57,00)		5564 (85,35)		4184 (39,54)	
Death event	16842	11907 (70,70)	6434	4565 (70,95)	10408	7342 (70,54)	0,5707
Median follow-up time in months (95% CI)	16842	30,23 (29,50-30,78)	4634	29,50 (28,81-30,49)	10408	30,62 (29,77-31,47)	0,0387

Propensity score

First step Multivariate logistic regression : probability to have lung metastases

		n	OR (95% CI)	pvalue
		10273		
Sex	Female vs Male		1,08 (0,99-1,19)	0,0915
Age, y	≥ 70 vs < 70		1,33 (1,20-1,47)	<0,0001
BMI	> 25 vs ≤ 25		1,30 (1,18-1,42)	<0,0001
ECOG PS	≥ 1 vs 0		0,87 (0,80-0,96)	0,0031
Tumor location				<0,0001
	Rectum vs colon		2,3 (2,08-2,54)	<0,0001
	Rectum + colon vs colon		1,53 (1,08-2,17)	<0,0001
No. of metastatic site	≥ 2 vs 1		9,05 (8,14-10,06)	<0,0001



Propensity score

Second step Propensity score applied in survival analysis

Based on previous models, overall survival was analyzed with

1- **IPTW method** : Cox regression is weighted according to the probability for patients to have lung metastases.

2- **Matched approach** : patients with lung metastases are matched with patients without lung metastases but with close propensity score in order to obtain 2 groups with similar characteristics. OS curves are estimated on this sample with the Kaplan-Meier method.

Propensity score

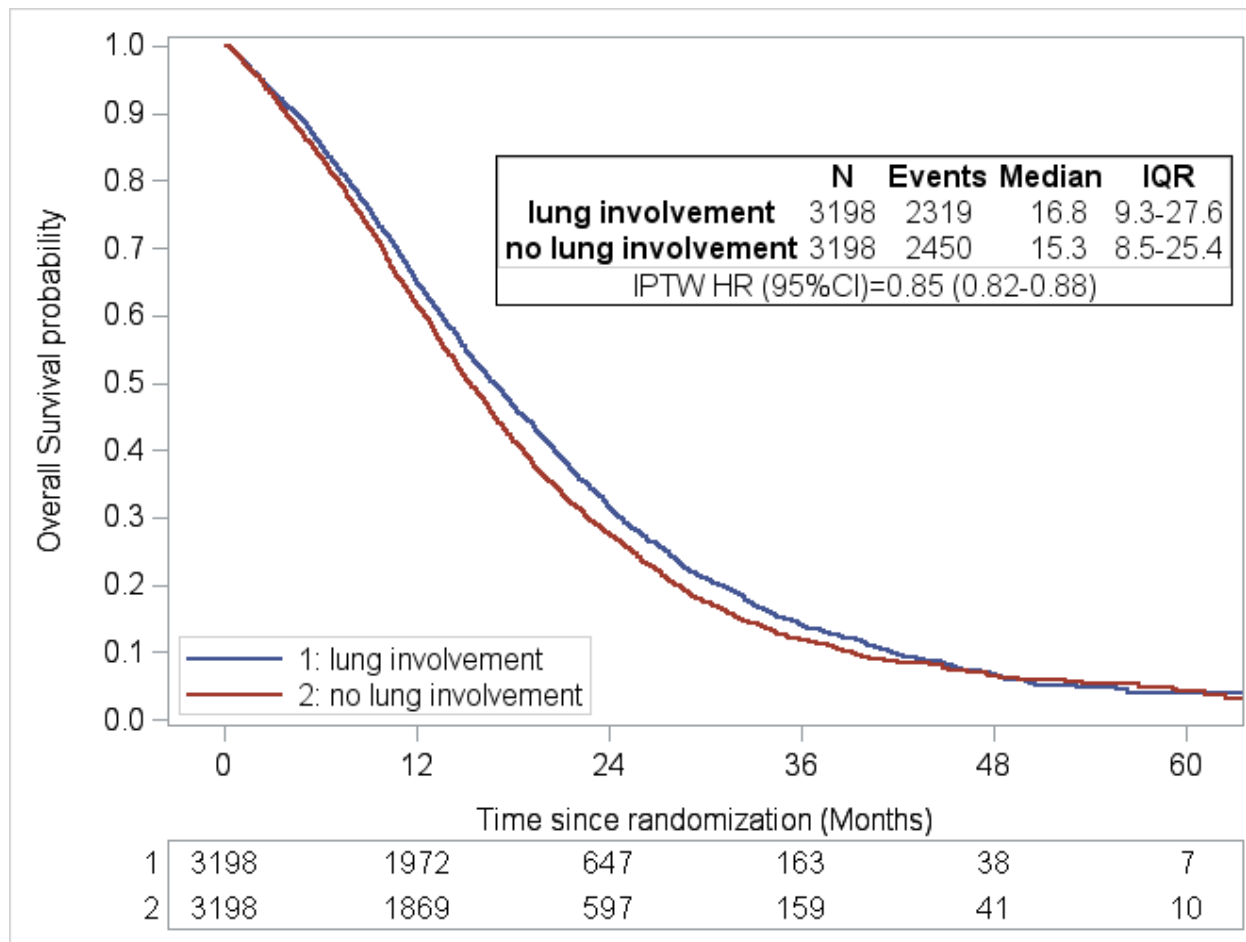
1:1 matched sample, caliper =0,05

Characteristic	Matched sample (n = 6396)		Population with lung metastasis (n = 3198)		Population without lung metastasis (n = 3198)		pvalue	Standardized differences
	No.	(%)	No.	(%)	No.	(%)		
Sex							0,64	-0,0116
	Male	3970 (62,1)	1994 (62,4)		1976 (61,8)			
	Female	2426 (37,9)	1204 (37,6)		1222 (38,2)			
Age, y							0,25	0,0291
	< 70	4707 (73,6)	2333 (73,0)		2374 (74,2)			
	≥ 70	1689 (26,4)	865 (27,0)		824 (25,8)			
BMI							0,41	0,0207
	≤ 25	2873 (44,9)	1420 (44,4)		1453 (45,4)			
	> 25	3523 (55,1)	1778 (55,6)		1745 (54,6)			
ECOG PS							0,37	0,0225
	0	3116 (48,72)	1540 (48,2)		1576 (49,3)			
	≥ 1	3280 (51,3)	1658 (51,8)		1622 (50,7)			
Tumor location							0,35	0,0363
	Colon	4535 (70,9)	2253 (70,4)		2282 (71,3)			
	Rectum	1766 (27,6)	891 (27,9)		875 (27,4)			
	Colon + rectum	95 (1,5)	54 (1,7)		41 (1,3)			
No. of metastatic site							1	0
	1	1102 (17,2)	551 (17,2)		551 (17,2)			
	≥ 2	5294 (82,8)	2647 (82,8)		2647 (82,8)			

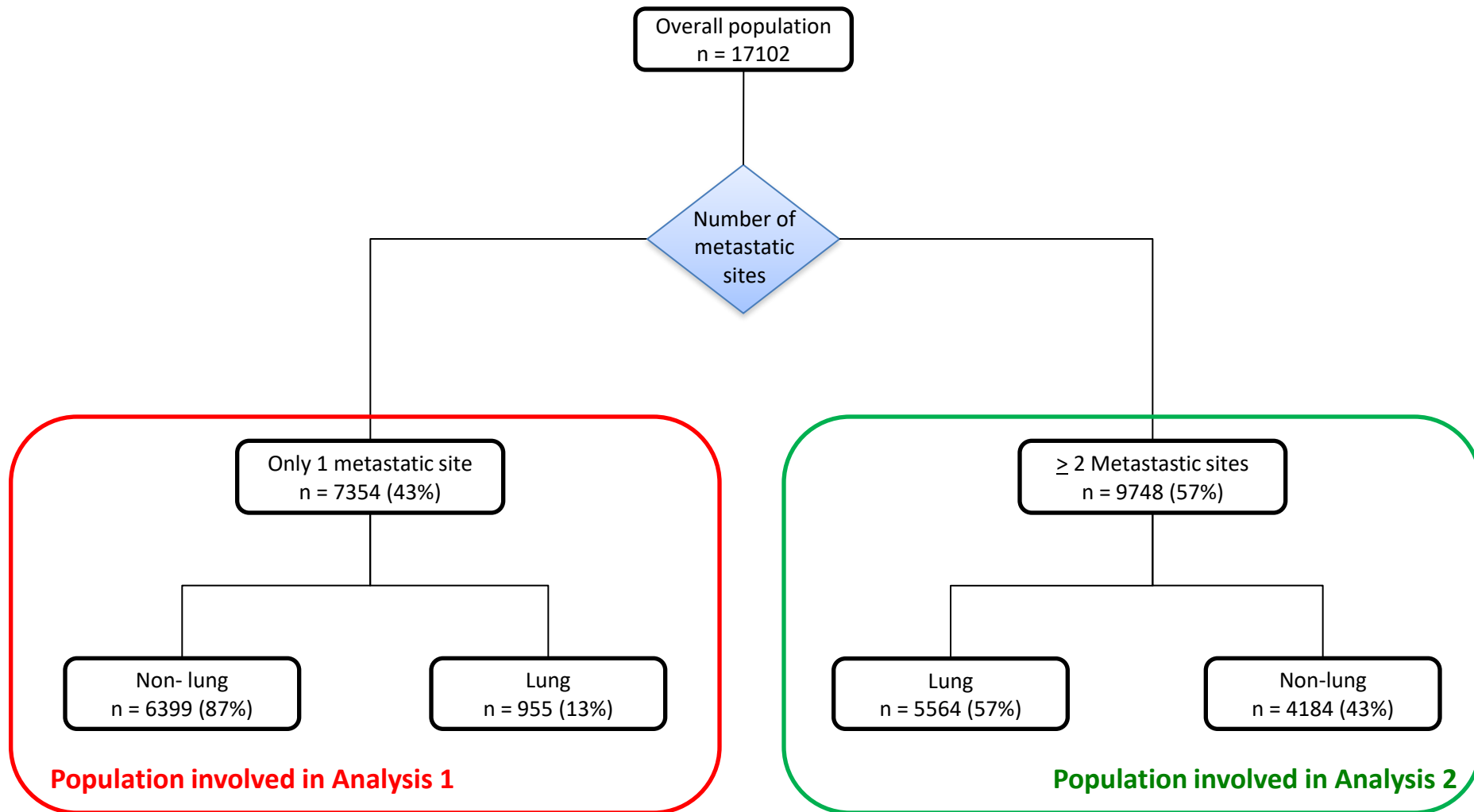
Overall Survival

Hazard ratio computed by applying the **IPTW** method in a **frailty Cox** regression with a random effect on trial

OS curves estimated with the **Kaplan-Meier method** in the **sample 1:1 matched** with the propensity score



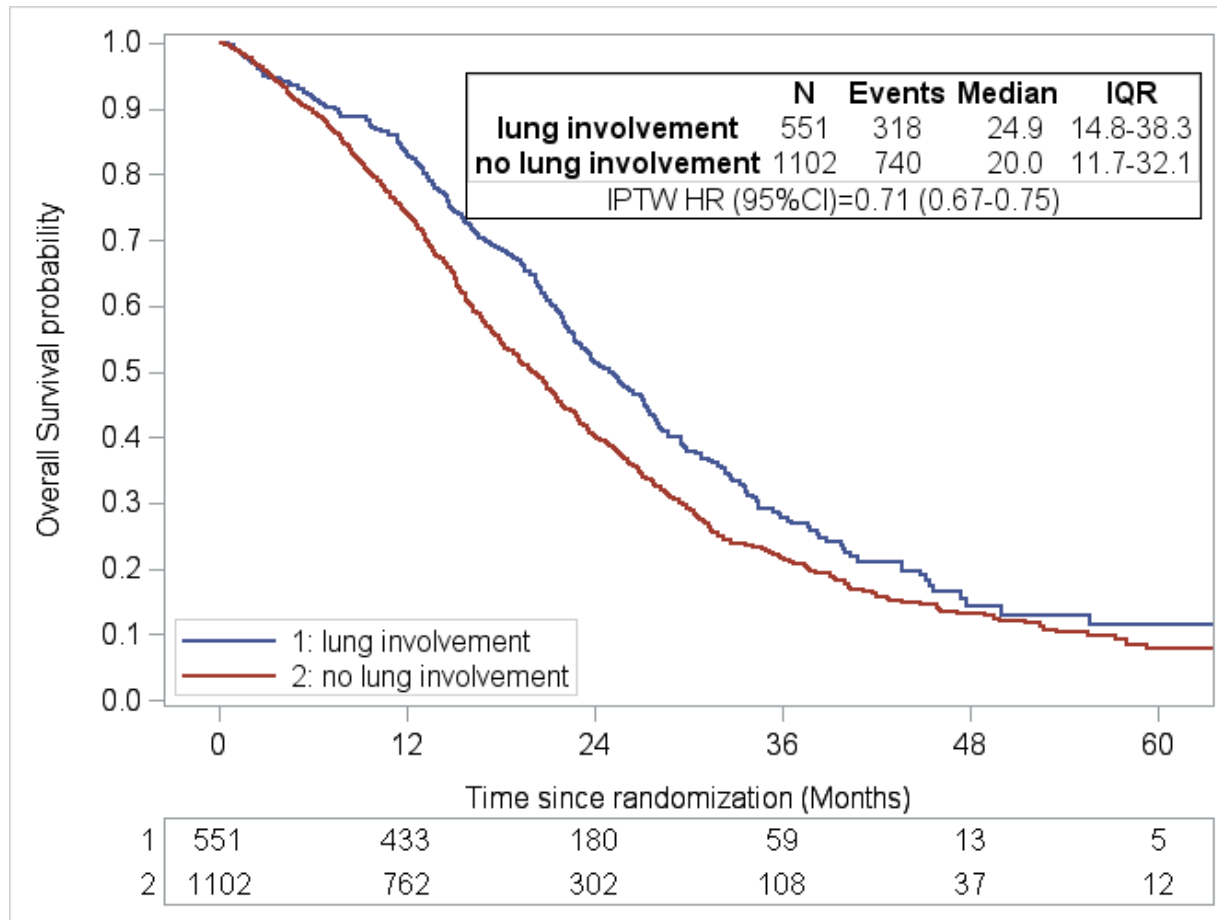
Population regarding number of metastatic sites



OS: only 1 metastatic site

Hazard ratio computed by applying the **IPTW** method in a **frailty Cox** regression with a random effect on trial

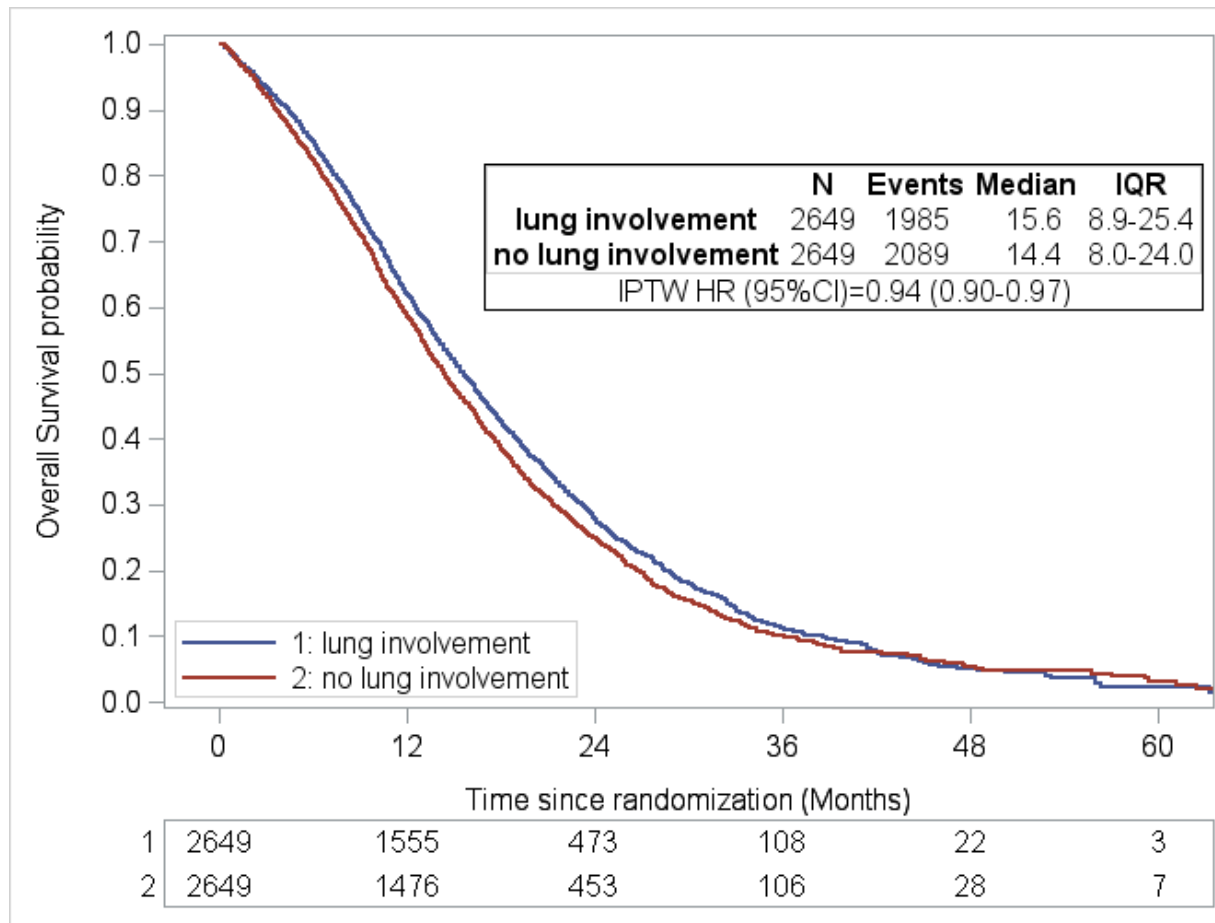
OS curves estimated with the **Kaplan-Meier method** in the **sample 1:2 matched** with the propensity score



OS \geq 2 metastatic sites

Hazard ratio computed by applying the **IPTW** method in a **frailty Cox** regression with a random effect on trial

OS curves estimated with the **Kaplan-Meier method** in the **sample 1:1 matched** with the propensity score



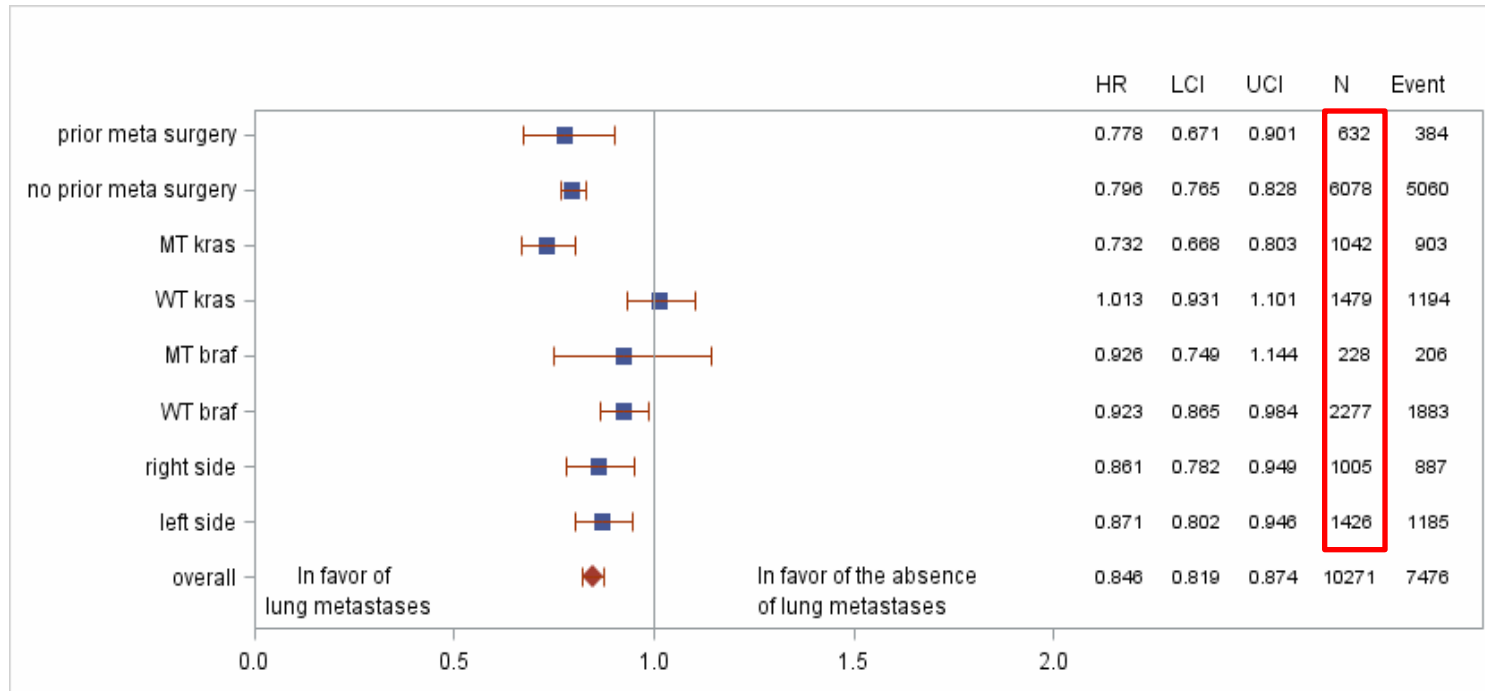
Subgroup analysis

characteristics	Overall population (n=17102)		Lung meta population (n = 6519)		No lung meta population (n = 10583)		pvalue
	N (%)	No. (%)	n	No. (%)	n	No. (%)	
Colon side Location	2708 (16)		917		1791		0,3801
Left		1619 (59,79)		556 (60,6)		1063 (59,3)	
Right		1085 (40,07)		361 (39,4)		724 (40,4)	
left + right		4 (0,15)		0 (0,0)		4 (0,2)	
BRAF	2943 (17)		1161		1782		0,0003
mutated		262 (8,90)		76 (6,5)		186 (10,4)	
wilded		2681 (91,10)		1085 (93,4)		1596 (89,6)	
KRAS	3245 (19)		1264		1981		<0,0001
mutated		1398 (43,08)		628 (49,7)		770 (38,9)	
wilded		1847 (56,92)		636 (50,3)		1211 (61,1)	
Prior meta surgery	7650 (45)		2976		4674		0,0258
No		6969 (91,10)		2684 (90,2)		4285 (91,7)	
Yes		681 (8,90)		292 (9,8)		389 (8,3)	

Subgroup analysis

Overall population

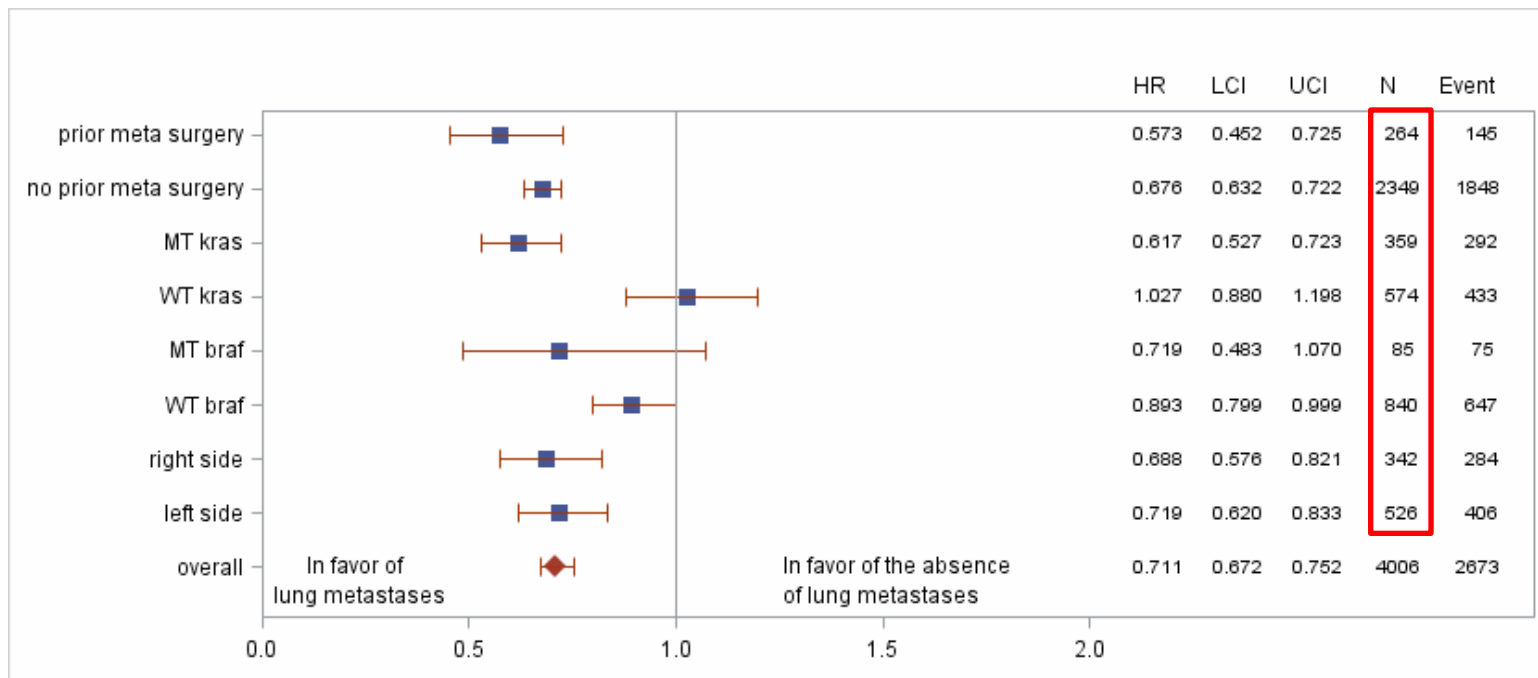
Association between lung metastases and OS estimated in each subgroup:
HR obtained with IPTW method applied in a frailty Cox



Subgroup analysis

Population with only 1 metastatic site

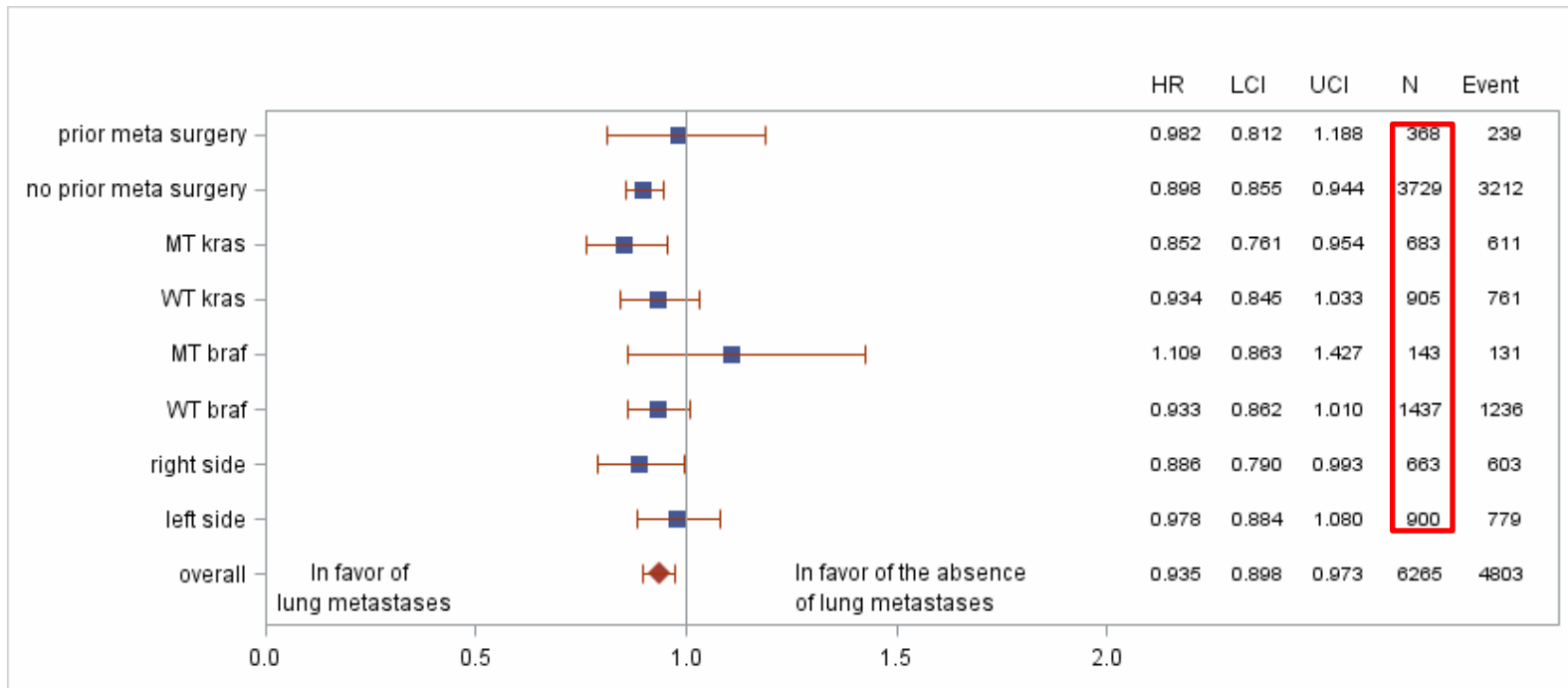
Association between lung metastases and OS estimated in each subgroup:
HR obtained with IPTW method applied in a frailty Cox



Subgroup analysis

Population with ≥ 2 metastatic sites

Association between lung metastases and OS estimated in each subgroup:
HR obtained with IPTW method applied in a frailty Cox



Conclusions

- There is significant prognostic heterogeneity among mCRC pts regarding the localization of metastases
- Lung metastasis, either as single or as part of multiple metastatic sites, have significantly better OS compared to those without lung involvement
- Trend for interaction between lung metastases and KRAS in population with only 1 metastatic site

Thank you for your attention

Patients characteristics

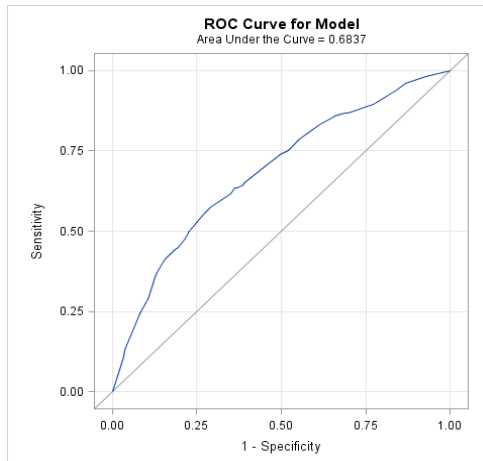
Overall population n=17 102		Only 1 metastatic site (n=7354, 43%)			≥2 metastatic sites (n=9748, 57%)		
		Lung meta population n=955 (13%)		No lung meta population n=6 399 (87%)	Lung meta population n=5 564 (57%)		No lung meta population n=4 184 (43%)
Characteristics	N	N	N	pvalue	N	N	pvalue
Gender	17091	955	6394	0,0637	5562	4180	0,1487
Male	10556 (61,76)	564 (59,06)	3976 (62,18)		3469 (62,37)	2547 (60,93)	
Female	6535 (38,24)	391 (40,94)	2418 (37,82)		2093 (37,63)	1633 (39,07)	
Age	17097	955	6398	<0,0001	5561	4183	<0,0001
Median	63	64	62		63	62	
Q1-Q3	55-69	56-70	54-69		56-70	54-69	
BMI	15600	835	5607	<0,0001	5202	3956	<0,0001
Median	25,36	26,47	25,22		25,59	25,08	
Q1-Q3	22,72-28,57	23,61-29,67	22,48-28,40		22,99-28,76	22,51-28,22	
PS OMS	16878	945	6281	<0,0001	5514	4138	0,8278
0	8925 (52,88)	608 (64,34)	3481 (55,42)		2768 (50,20)	2068 (49,98)	
>=1	7953 (47,12)	337 (35,66)	2800 (44,58)		2746 (49,80)	2070 (50,02)	
Tumor location	11587	657	4164	<0,0001	3909	2857	<0,0001
Colon	8024 (69,25)	314 (47,79)	3076 (73,87)		2452 (62,73)	2182 (76,37)	
Rectum	3378 (29,15)	331 (50,38)	1005 (24,14)		1399 (35,79)	643 (22,51)	
Colon +rectum	185 (1,60)	12 (1,83)	83 (1,99)		58 (1,48)	32 (1,12)	

Propensity score

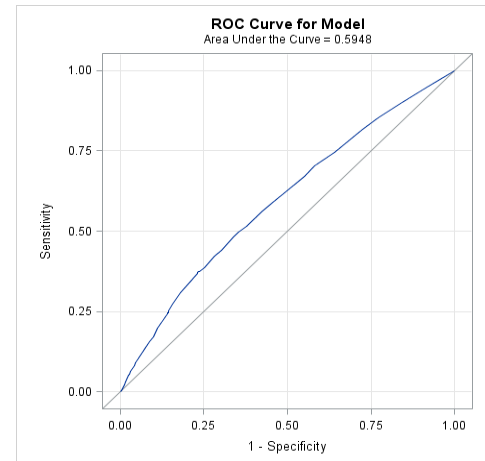
First step Multivariate logistic regression : probability to have lung metastases

		Only 1 metastatic site			≥2 metastatic sites		
		n	OR (CI 95%)	pvalue	n	OR (CI 95%)	pvalue
		4007			6266		
Gender	Female vs Male		1,36 (1,12-1,64)	0,002		1,01 (0,91-1,13)	0,792
Age in years	>=70 vs < 70		1,46 (1,19-1,79)	0,0002		1,28 (1,14-1,44)	<0,0001
BMI	>25 vs <=25		1,51 (1,25-1,83)	<0,0001		1,23 (1,11-1,37)	<0,0001
PS	>=1 vs 0		0,63 (0,52-0,77)	<0,0001		0,96 (1,12-2,71)	0,425
Tumor location				<0,0001			<0,0001
	rectum vs colon		3,37 (2,79-4,08)	<0,0001		1,99 (1,78-2,23)	<0,0001
	rectum+colon vs colon		1,26 (0,64-2,46)	0,5102		1,74 (1,12-2,71)	0,0142

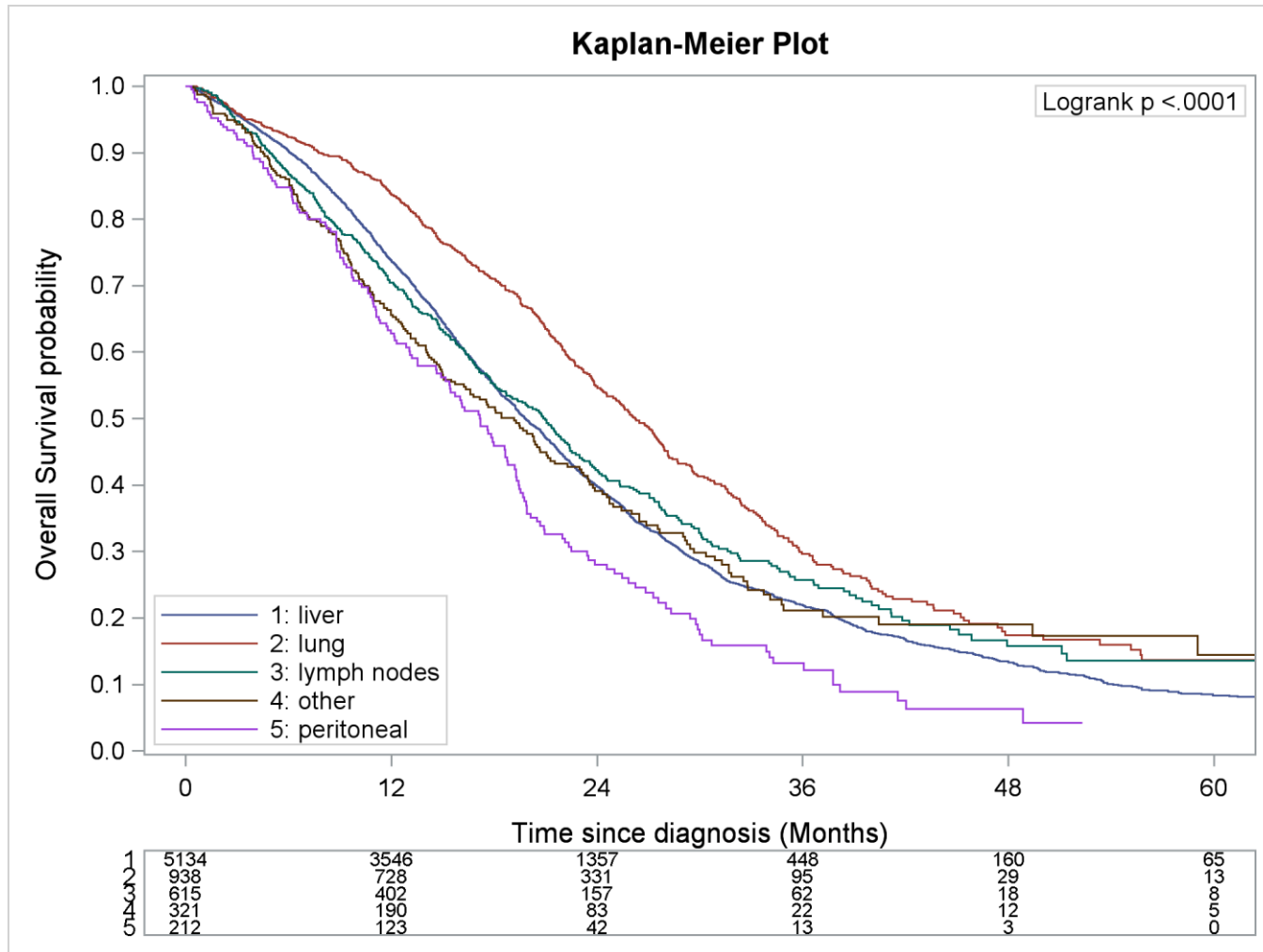
Only 1 metastatic site



≥2 metastatic sites



OS : Only 1 metastatic site



Subgroup analysis

characteristics	Overall population (n=17102) N (%)	Only 1 metastatic site (n=7354)			≥2 metastatic sites (n=9748)		
		Lung meta population (N=955) N (%)	No lung meta population (N=6399) N		Lung meta population (N=5564) N	No lung meta population (N=4184) N	
				pvalue			pvalue
Colon side Location	2708 (16)	100	953	0,3385	817	838	0,1657
Left	1619 (59,79)	69 (69,00)	589 (61,80)		487 (59,61)	474 (56,56)	
Right	1085 (40,07)	31 (31,00)	362 (37,99)		330 (40,39)	362 (43,20)	
left + right	4 (0,15)	0 (0)	2 (0,21)		0 (0)	2 (0,24)	
BRAF	2943 (17)	138	935	0,145	1023	847	0,0004
mutated	262 (8,90)	8 (5,80)	90 (9,63)		68 (6,65)	96 (11,33)	
wilded	2681 (91,10)	130 (94,20)	845 (90,37)		955 (93,35)	751 (88,67)	
KRAS	3245 (19)	154	1067	<0,0001	1110	914	0,001
mutated	1398 (43,08)	94 (61,04)	397 (37,21)		534 (48,11)	373 (40,81)	
wilded	1847 (56,92)	60 (38,96)	670 (62,79)		576 (51,89)	541 (59,19)	
Prior meta surgery	7650 (45)	430	2602	0,8388	2546	2072	<0,0001
No	6969 (91,10)	386 (89,77)	2344 (90,08)		2298 (90,26)	1941 (93,68)	
Yes	681 (8,90)	44 (10,23)	258 (9,92)		248 (9,74)	131 (6,32)	

Material and Methods

Material

- ARCAD* Foundation database
- Selection of trials :
 - First-line prospective controlled randomized phase III trials
 - Information about lung metastases and number of metastatic sites

Method

- Endpoint : OS : randomization to death from any cause
- Propensity score to model the probability to have lung metastases
 - To deal with confounding prognostic factors unequally distributed among groups
- Cox proportional hazard model
 - Heterogeneity between trials : frailty cox regression with random effect on trial and
 - Heterogeneity between patients with and without lung metastases:
 - Inverse Probability of treatment Weighted (IPTW) approach
- Single Kaplan Meier curve analysis
 - Sample matched with the propensity score (Caliper method)