

# 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% <sup>[1-2]</sup>
- Retrospective data confusing – some report better OS, other worse <sup>[3-4]</sup>

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

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

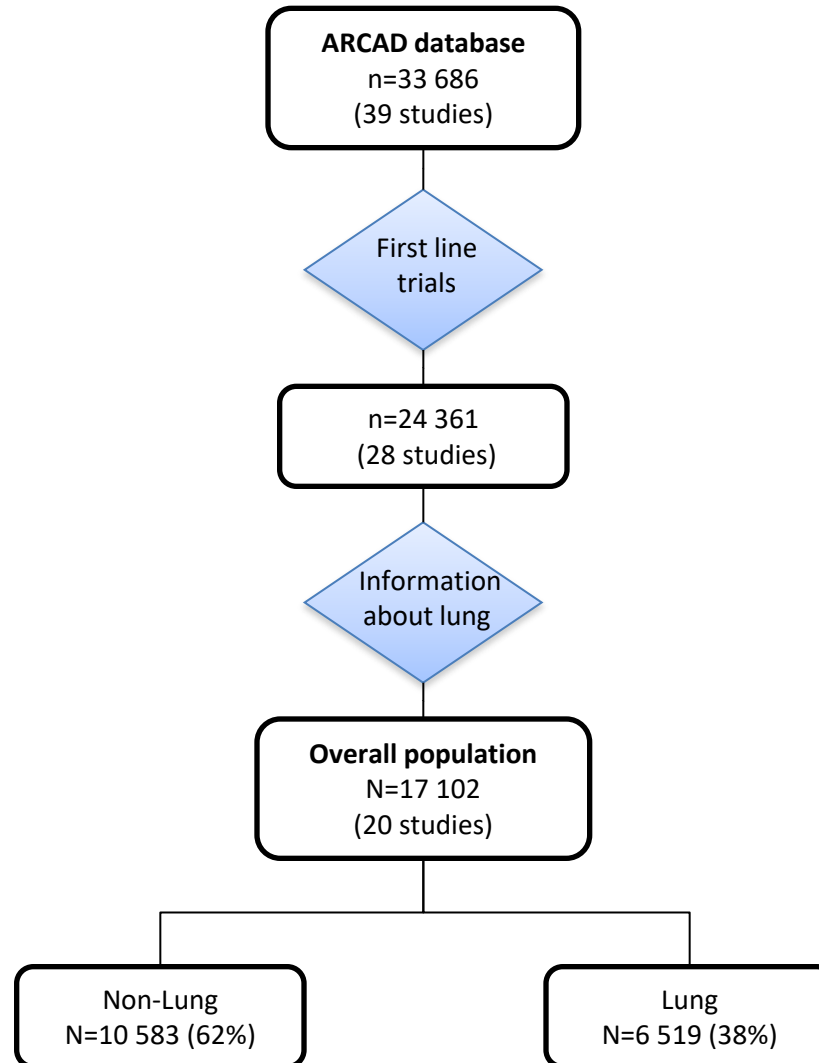
3. Lemmens et al *Int. J. Cancer* 2011, 128, 2717–2725

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

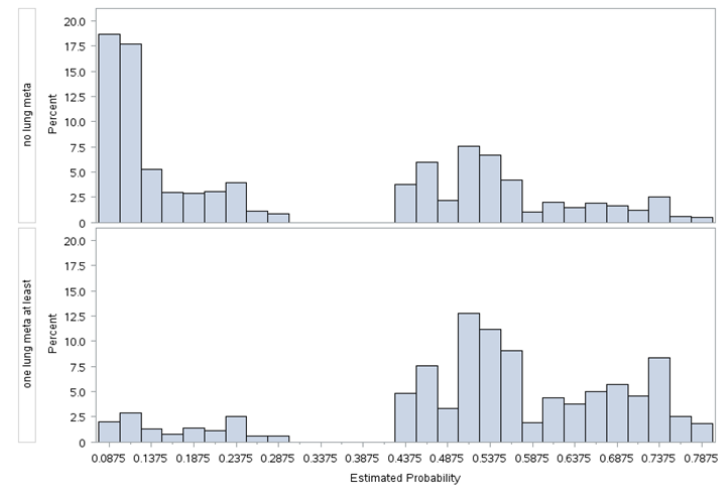
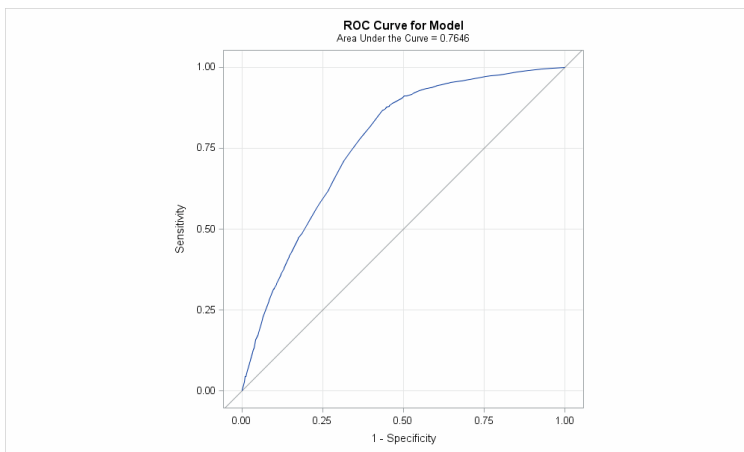
# Patients characteristics

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

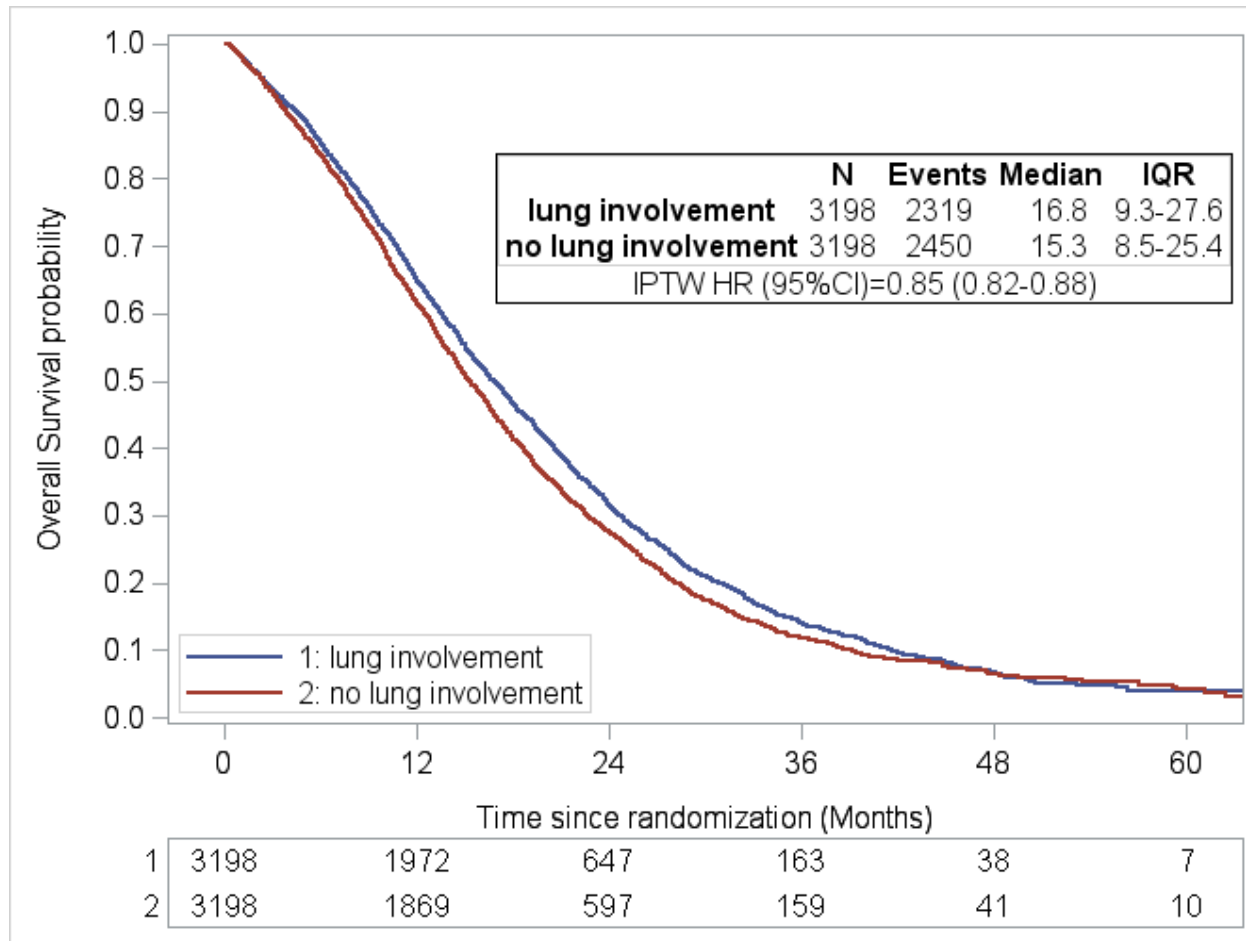
1:1 matched sample, caliper =0,05

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)			

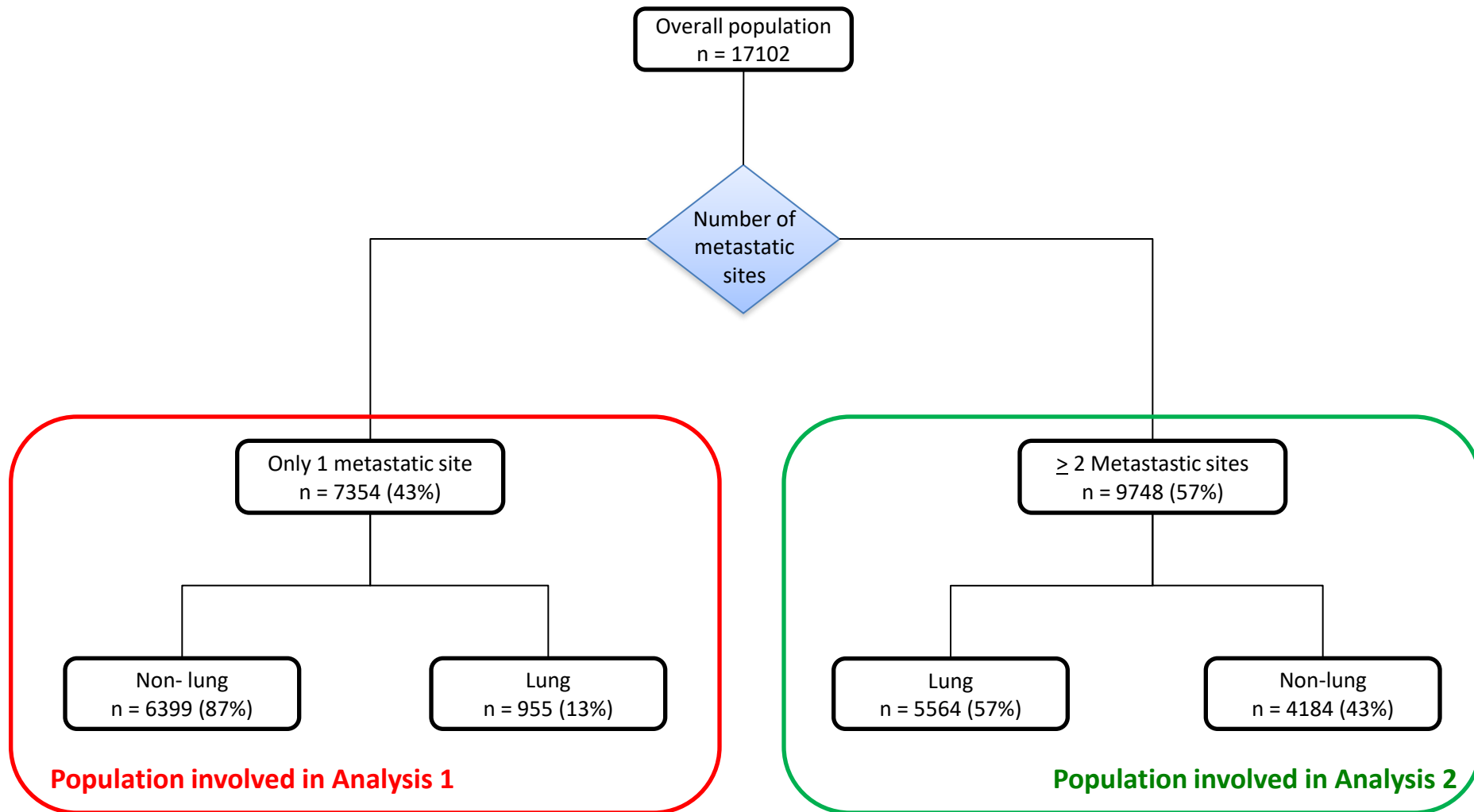
# Overall Survival

**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



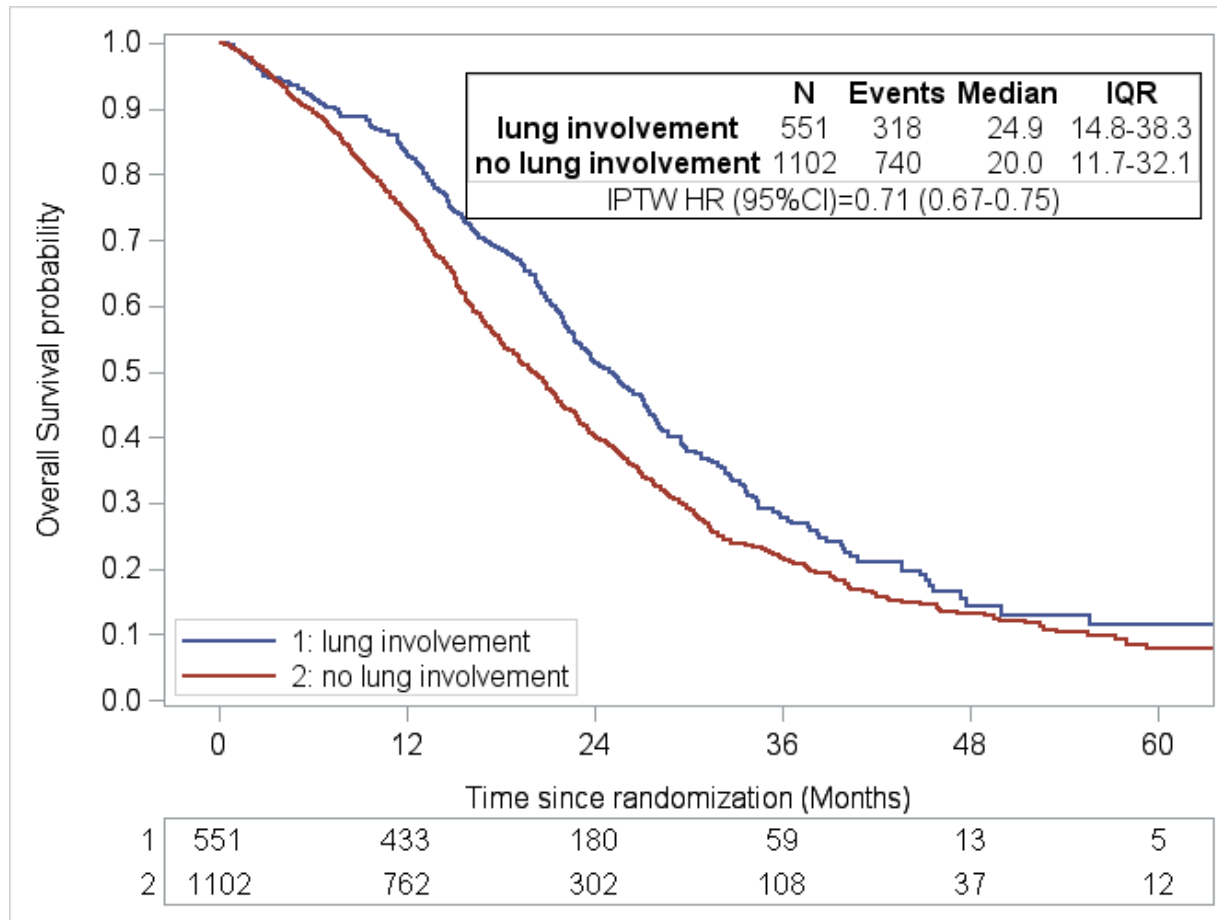
# Population regarding number of metastatic sites



# OS: only 1 metastatic site

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

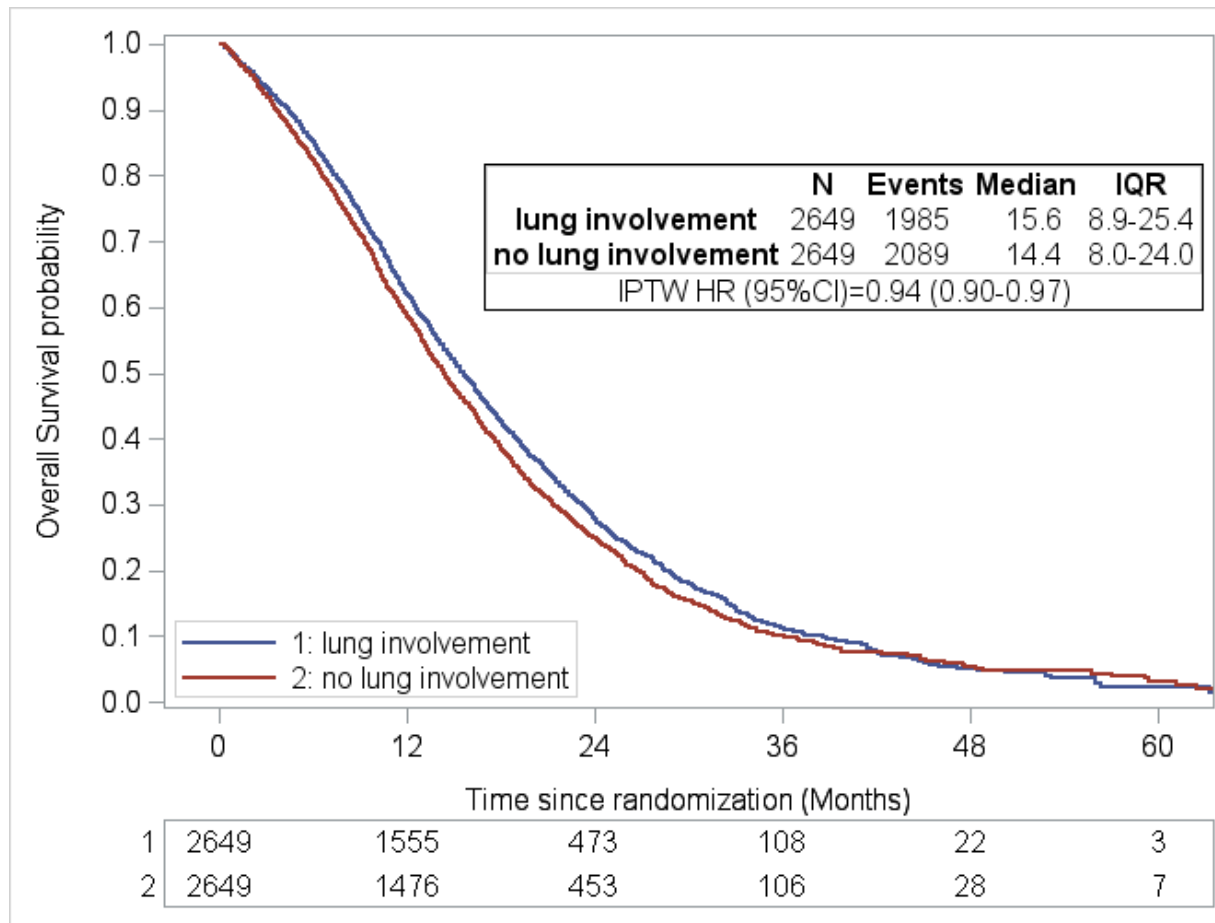
**OS curves** estimated with the **Kaplan-Meier method** in the **sample 1:2 matched** with the propensity score



# 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



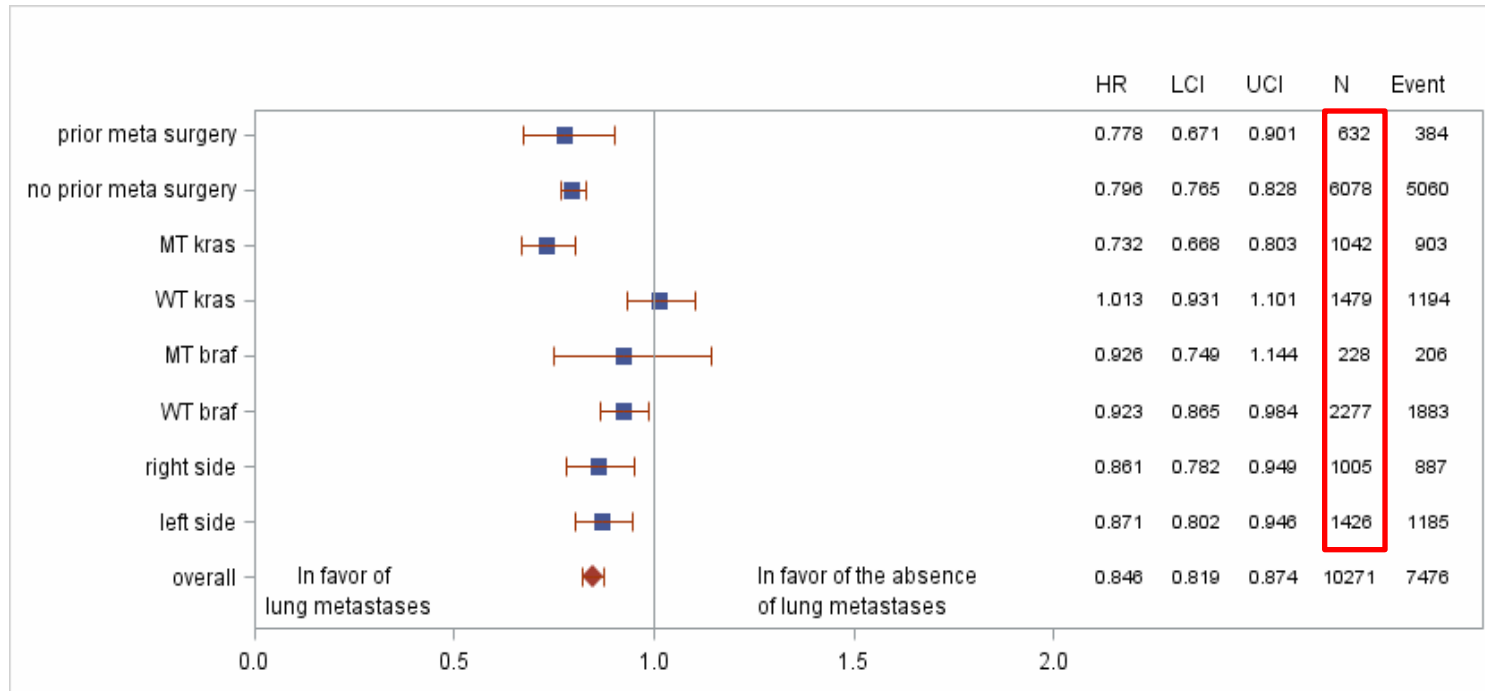
# Subgroup analysis

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

# Subgroup analysis

## Overall population

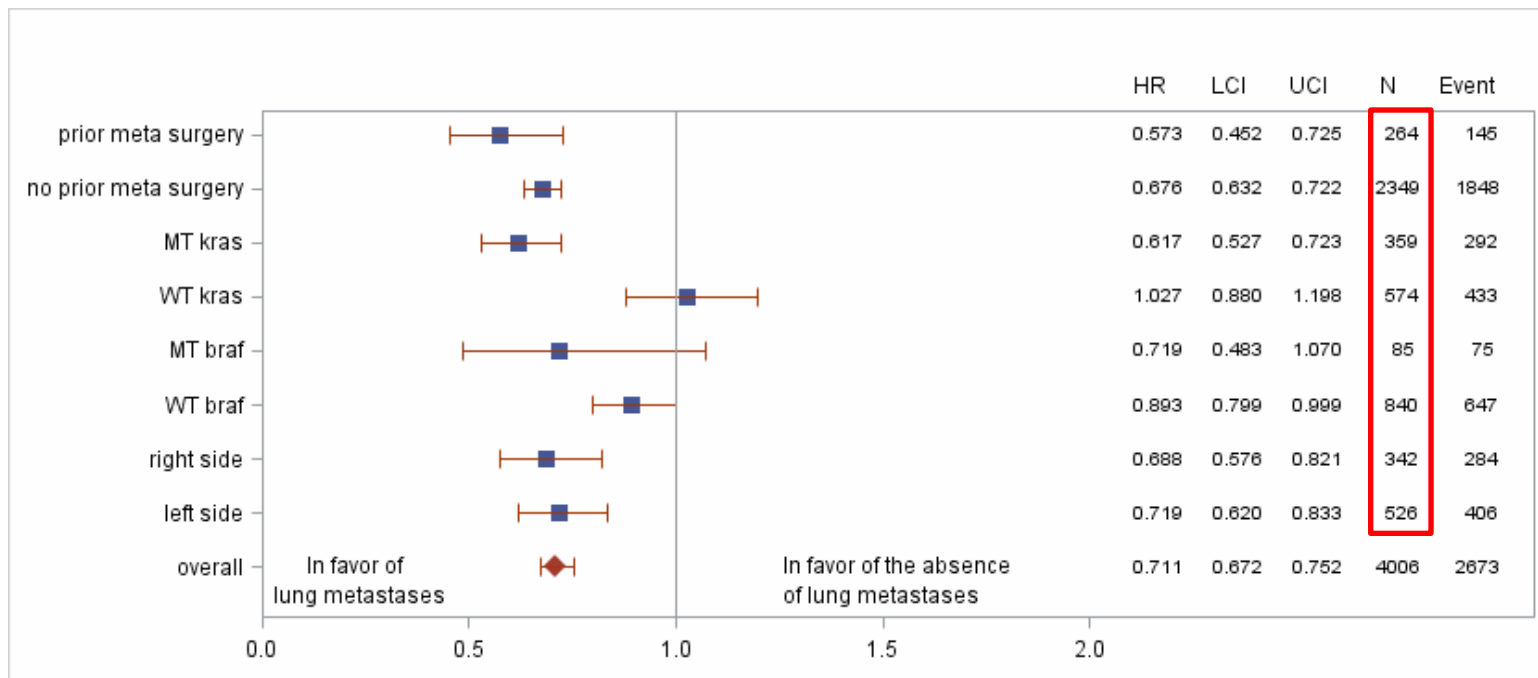
Association between lung metastases and OS estimated in each subgroup:  
HR obtained with IPTW method applied in a frailty Cox



# 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

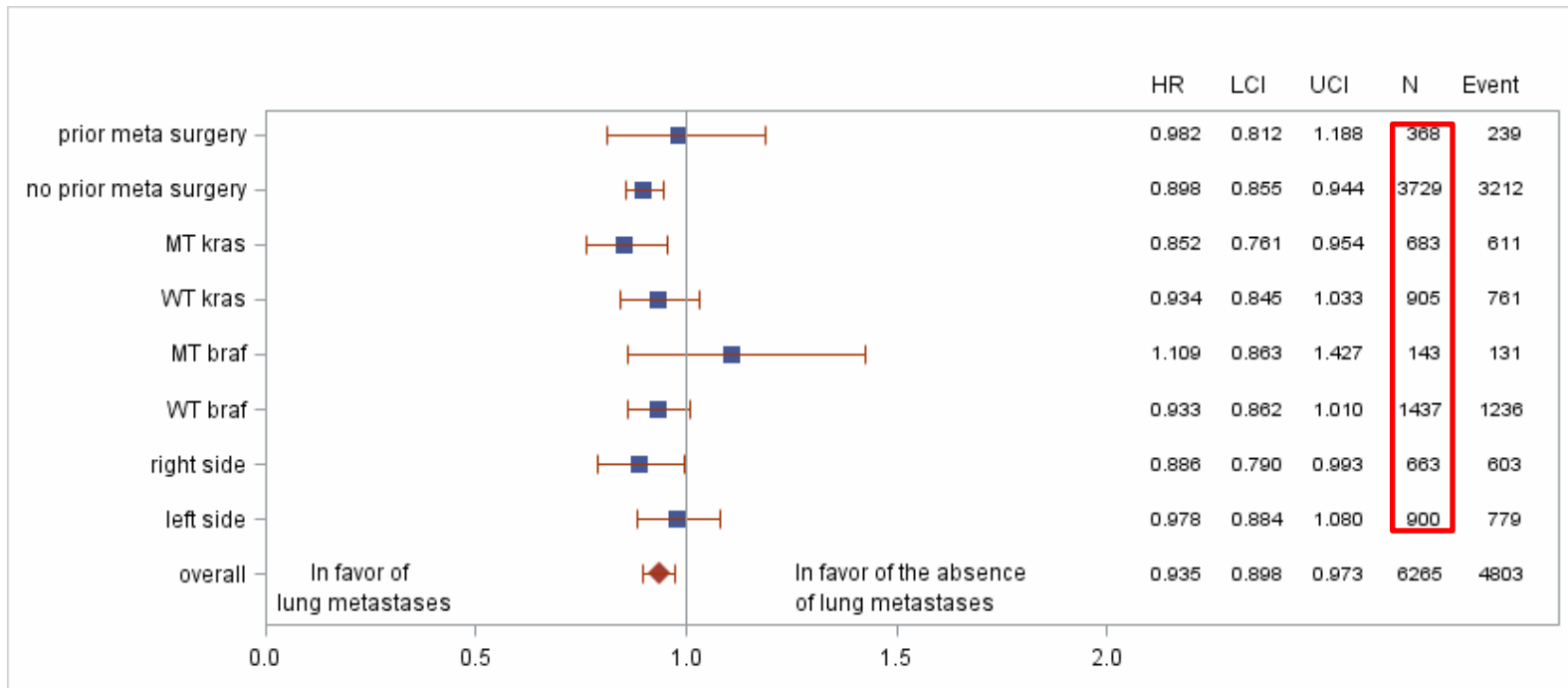




# Subgroup analysis

## Population with $\geq 2$ 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

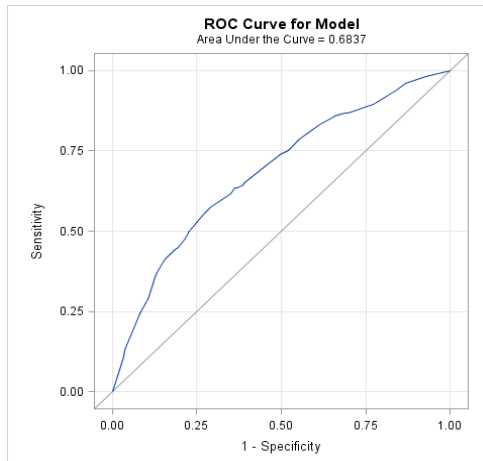
Overall population n=17 102		Only 1 metastatic site (n=7354, 43%)			≥2 metastatic sites (n=9748, 57%)		
		Lung meta population n=955 (13%)		No lung meta population n=6 399 (87%)	Lung meta population n=5 564 (57%)		No lung meta population n=4 184 (43%)
Characteristics	N	N	N	pvalue	N	N	pvalue
<b>Gender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

# Propensity score

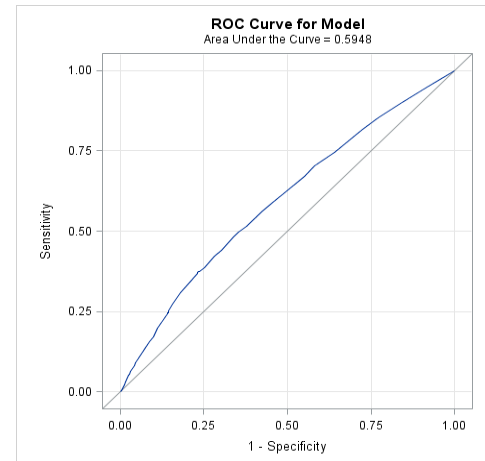
**First step** Multivariate logistic regression : probability to have lung metastases

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

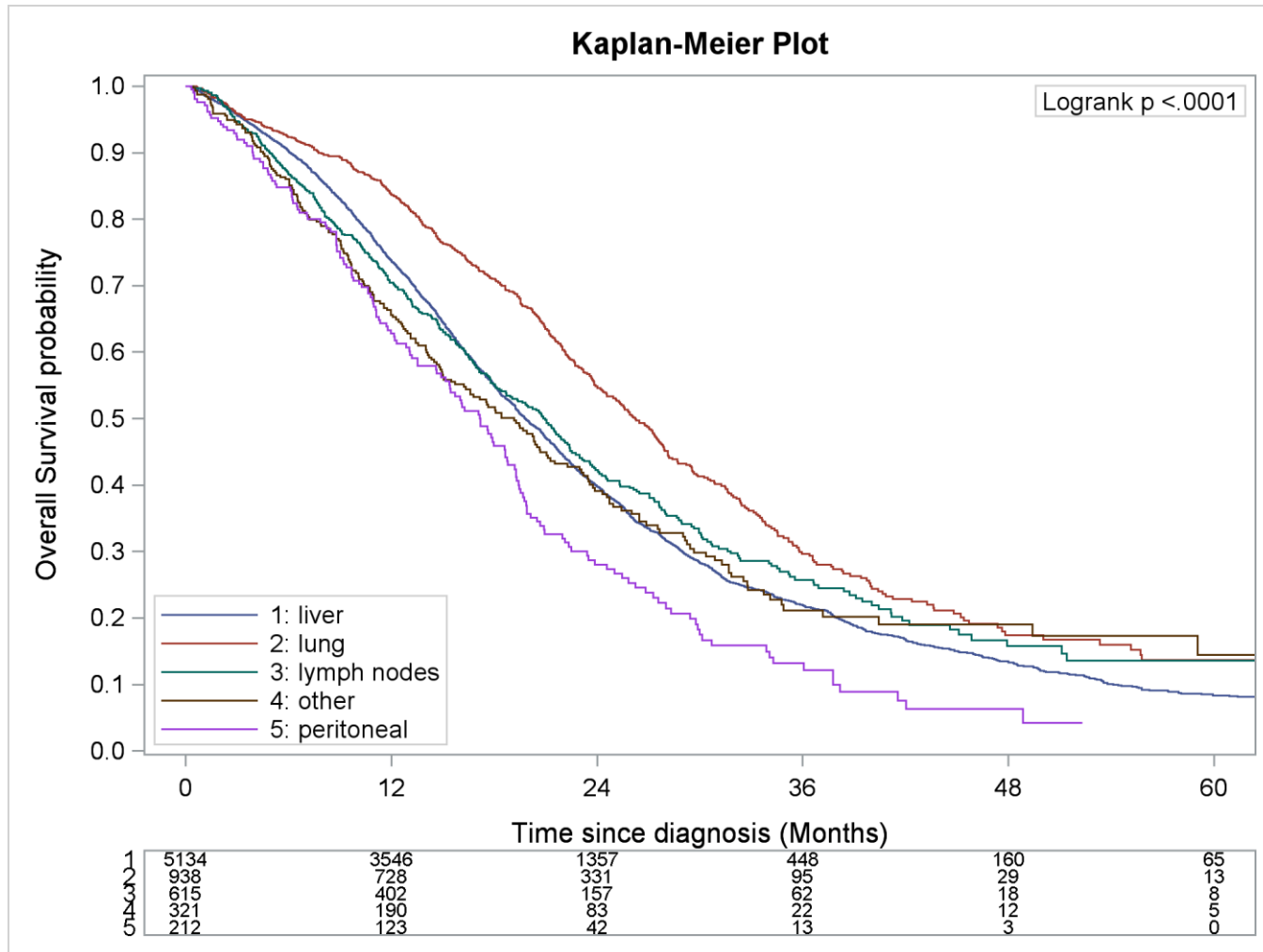
Only 1 metastatic site



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