

Management of Oligoprogressive Liver Metastases



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What is Oligo-metastatic disease ?

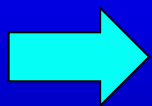
- The concept of oligometastatic disease (OMD) was first described in 1995 as an **intermediate state between locally confined and systemically metastasized cancer** (*Hellman S., J Clin Oncol 1995*).
- Entity potentially suitable for additional local or locoregional treatments with **curative intent** (*Kaneda Cancer Treat. Commun. 2015*)
- Defining OMD has been a **challenge**, and heterogeneity surrounding the definition of OMD has been a barrier to the standardization of clinical study protocols ($\leq 3, 4, 5$ metastases... 1 to 3 metastatic sites...) (*Adnan et al, Br J Radiol 2022*)

What is Oligo-metastatic disease ?

ESMO Clinical Practice Guideline (*Cervantes et al Ann Oncol 2022*)

A traditional clinical definition of OMD is:

- 1 to 5 metastatic lesions... occasionally more... if complete eradication is possible
- Up to 2 metastatic sites
- Controlled primary tumor (optionally resected)
- All metastatic sites must be safely treatable

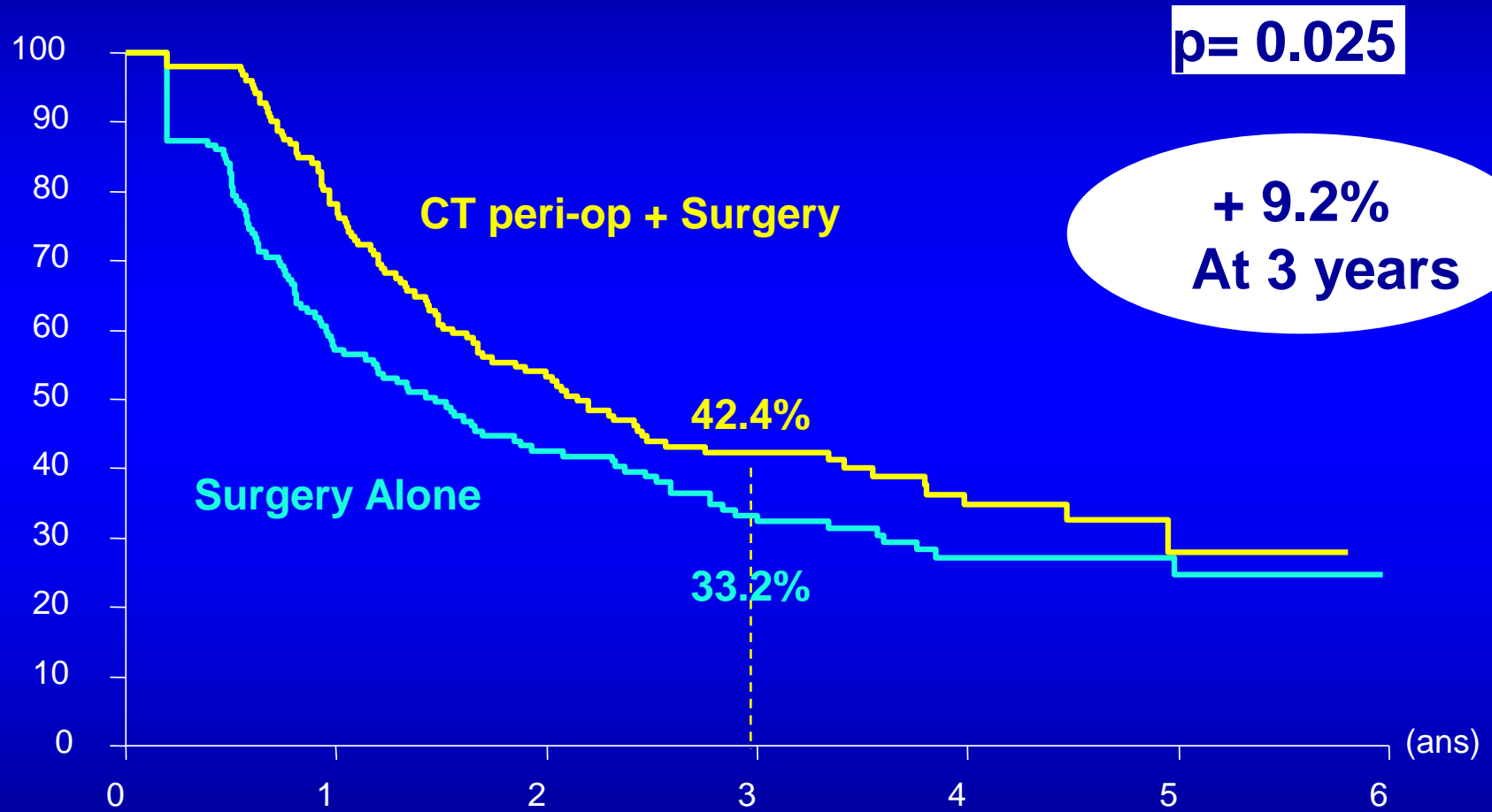
 Owing to the heterogeneity of the definition, would it not be more clinically relevant to rely on the usual 3 categories of patients:

- Upfront resectable (or locally treatable...)
- Marginally resectable
- Definitely unresectable

Management of Oligo-Progressive Colorectal Liver Metastases

1. Is chemotherapy always indicated for OMD ?
2. What are the objectives ?
3. What is the best treatment ?
4. What impact of progression on the management
5. Take-Home messages

Perioperative chemotherapy improve DFS in resectable patients **with ≤ 4 metastases**

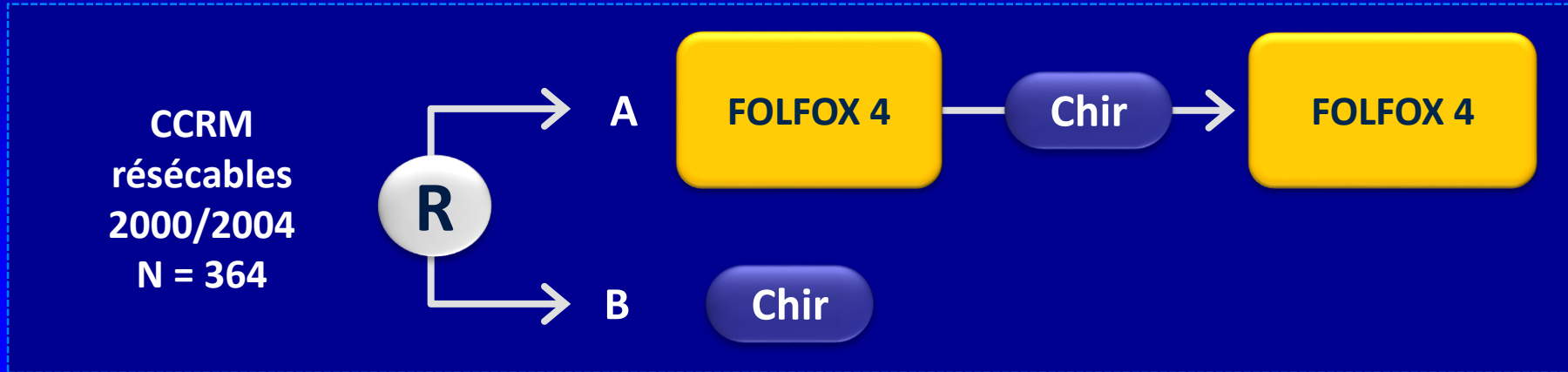


O	N	Number of patients at risk :			
104	152	85	59	39	24
93	151	118	76	45	23

Nordlinger Lancet 2008

EORTC/EPOC news : long term survival !

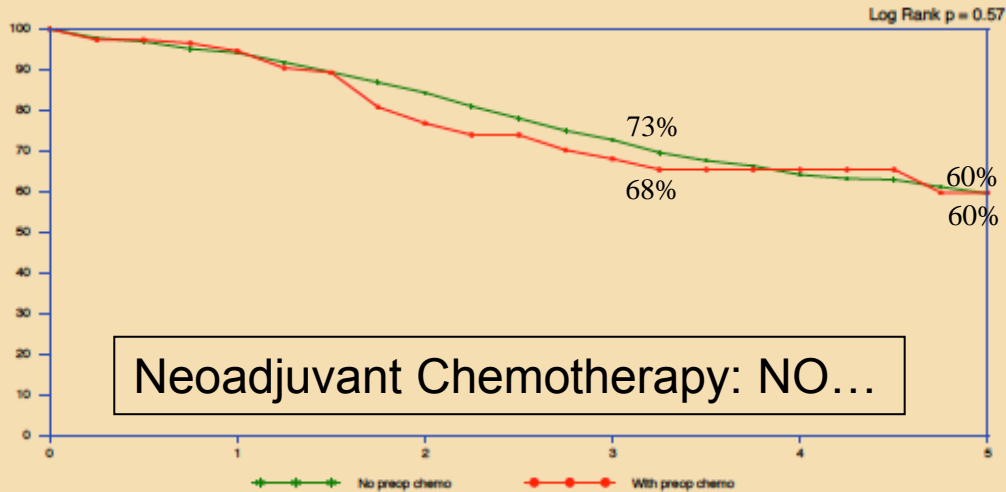
- Updating with Follow up at 8.5 yrs



- Improvement of PFS (Lancet 2008)
- **No improvement of OS, HR : 0.88 ($p = 0.34$)**
 - ITT median : 61 vs 54 months and at 5 yrs 51.2 vs 47.8%
 - Per protocol : 64 vs 55 months and at 5 yrs 52.4 vs 48.3%

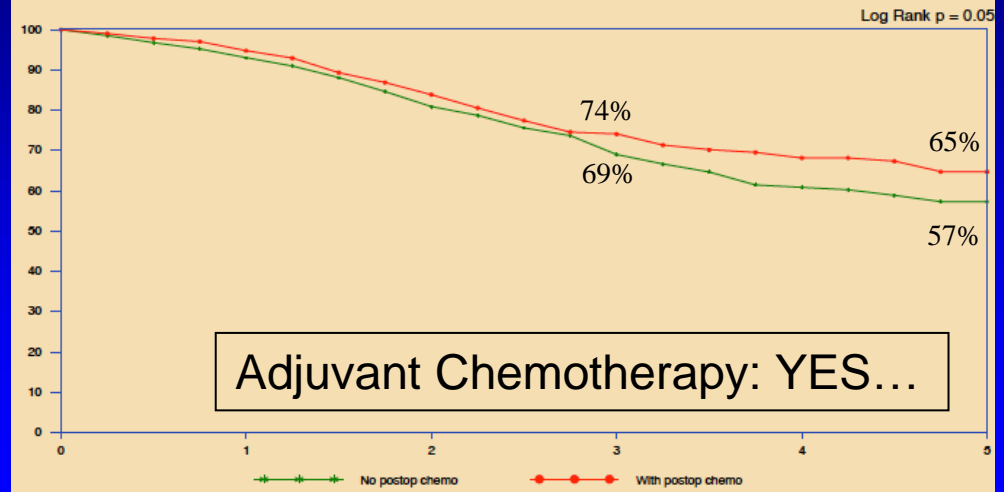
Is Chemotherapy useful for Single Metachronous Metastases ?

Patient Survival after a 1st hepatectomy for Colorectal Metastases : 1450 patients



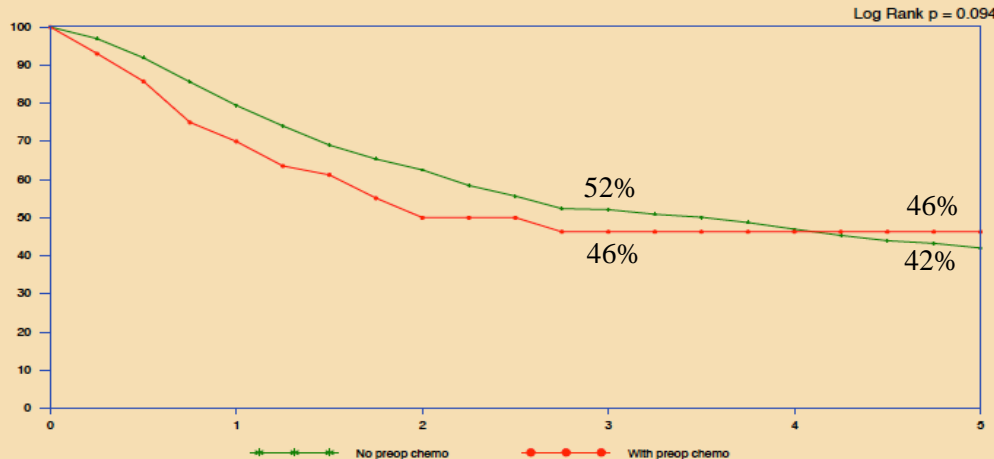
	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No preop chemo	1282	861	549	335	224	148
With preop chemo	168	95	56	28	13	8

Patient Survival after a 1st hepatectomy (2 months after) for Colorectal Metastases : 1063 patients



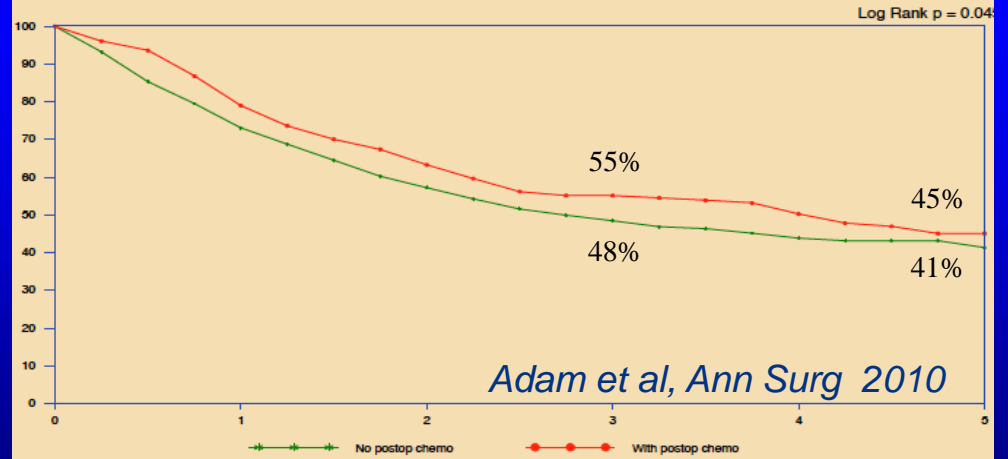
	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No postop chemo	622	434	272	151	101	64
With postop chemo	441	322	211	144	94	63

Patient Survival after a 1st hepatectomy for Colorectal Metastases : 1355 patients



	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No preop chemo	1198	680	383	221	154	100
With preop chemo	157	68	39	20	10	6

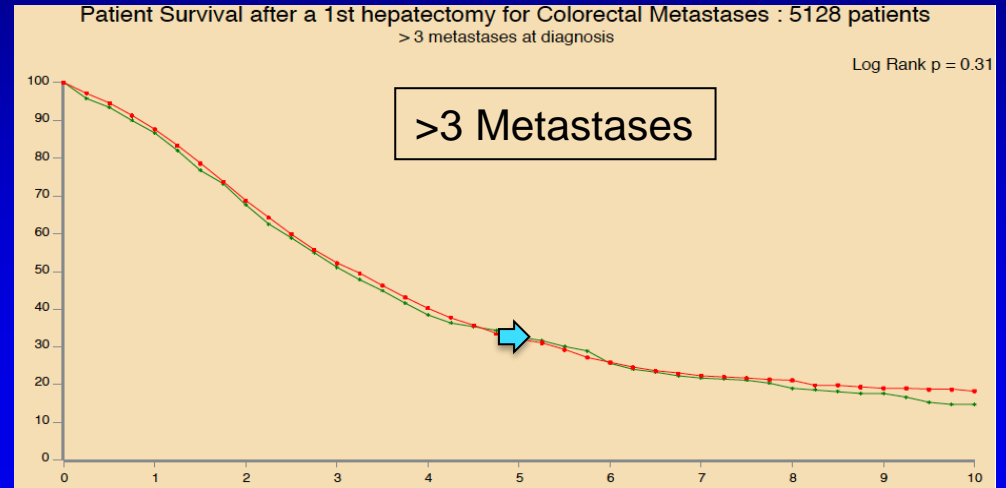
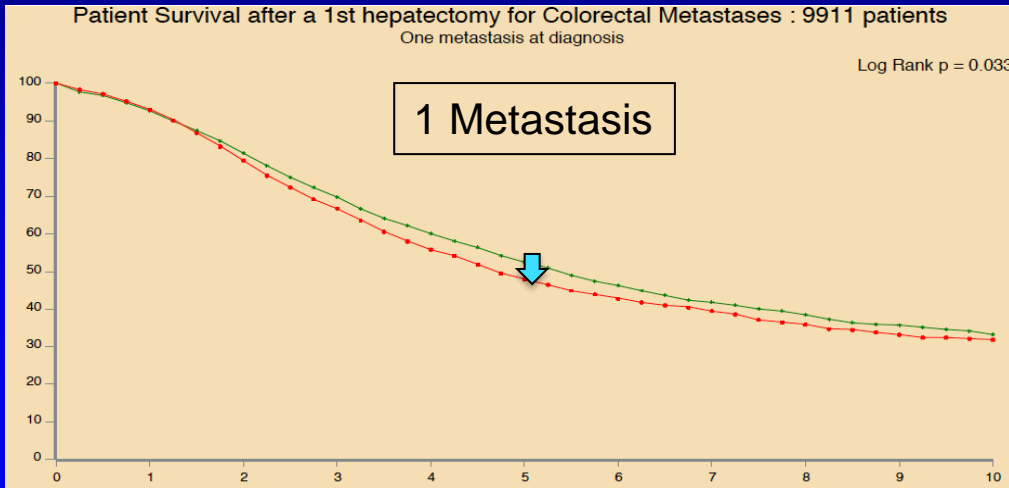
Patient Survival after a 1st hepatectomy (2 months after) for Colorectal Metastases : 972 patients



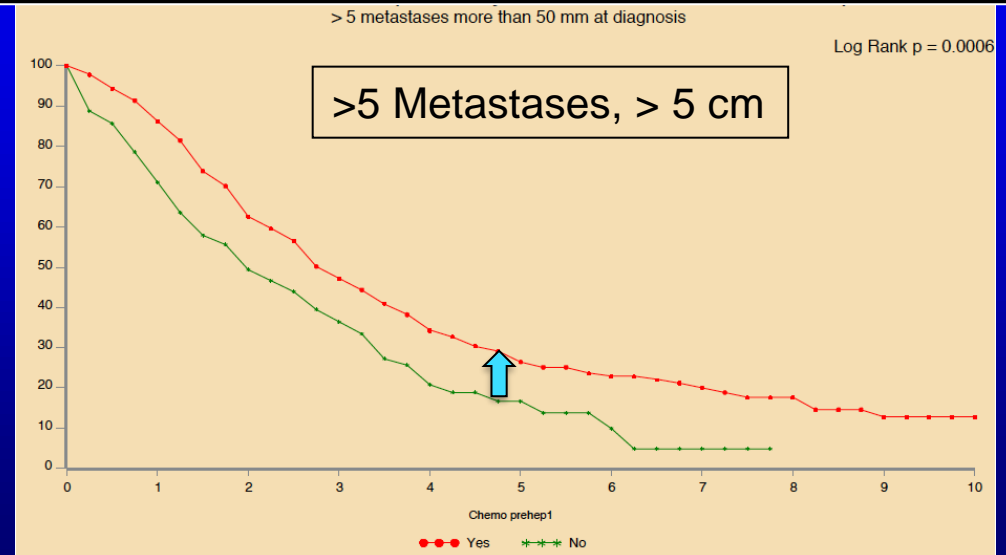
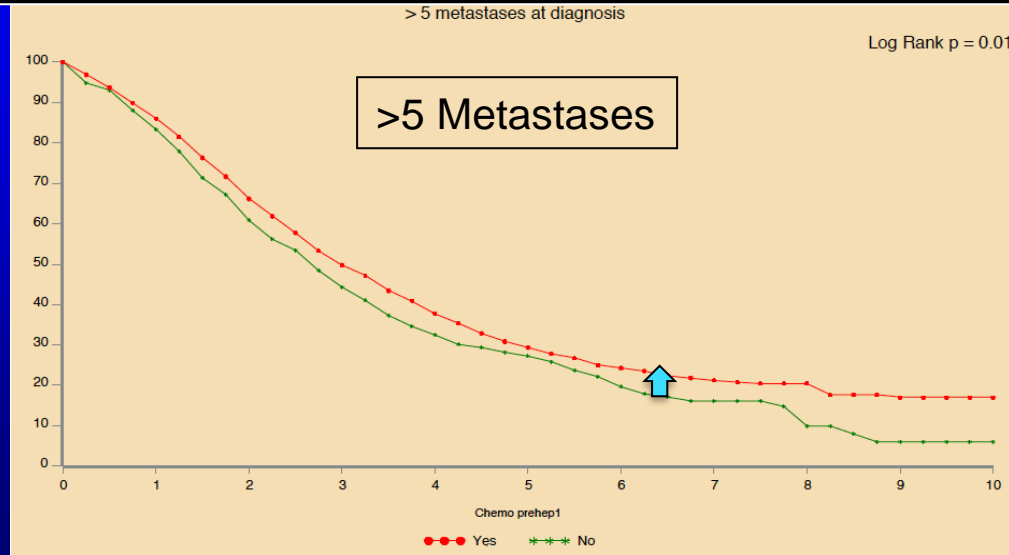
	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No postop chemo	579	318	182	94	66	42
With postop chemo	393	243	146	97	65	44

LIVERMETSURVEY June 2021

Role of Preop Chemotherapy vs Number and Size



The more extended the disease, the most useful the chemo



Is chemotherapy always indicated for Oligo-metastatic disease ?

ESMO Clinical Practice Guideline (*Cervantes et al Ann Oncol 2022*)

- In patients with resectable metastases and with favorable prognostic criteria and a good surgical approach, **perioperative systemic treatment may not be needed** [III,B].
- In patients with resectable metastases, the use of perioperative oxaliplatin-based ChT is **recommended where the prognostic situation is unclear** [II, B].

Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial

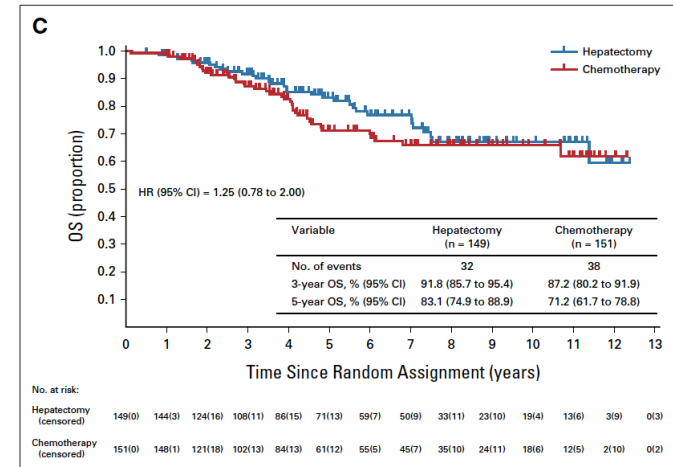
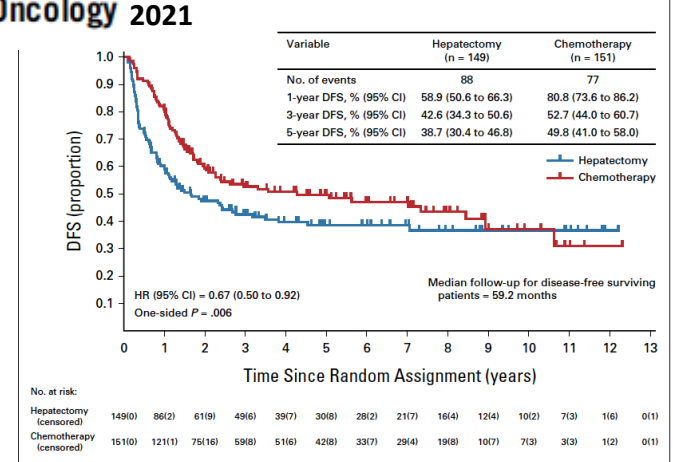
Yukihide Kanemitsu, MD¹; Yasuhiro Shimizu, MD, PhD²; Junki Mizusawa, ME¹; Yoshitaka Inaba, MD, PhD²; Tetsuya Hamaguchi, MD, PhD³; Dai Shida, MD, PhD¹; Masayuki Ohue, MD, PhD⁴; Koji Komori, MD, PhD²; Akio Shiomi, MD⁵; Manabu Shiozawa, MD, PhD⁶; Jun Watanabe, MD, PhD⁷; Takeshi Suto, MD⁸; Yusuke Kinugasa, MD, PhD⁹; Yasumasa Takii, MD¹⁰; Hiroyuki Bando, MD, PhD¹¹; Takaya Kobatake, MD¹²; Masafumi Inomata, MD, PhD¹³; Yasuhiro Shimada, MD¹⁴; Hiroshi Katayama, MD¹; and Haruhiko Fukuda, MD¹ on behalf of the JCOG Colorectal Cancer Study Group

PURPOSE Adjuvant chemotherapy after hepatectomy is controversial in liver-only metastatic colorectal cancer (CRC). We conducted a randomized controlled trial to examine if adjuvant modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) is superior to hepatectomy alone for liver-only metastasis from CRC.

PATIENTS AND METHODS In this phase II or III trial (JCOG0603), patients age 20-75 years with confirmed CRC and an unlimited number of liver metastatic lesions were randomly assigned to hepatectomy alone or 12 courses of adjuvant mFOLFOX6 after hepatectomy. The primary end point of phase III was disease-free survival (DFS) in intention-to-treat analysis.

RESULTS Between March 2007 and January 2019, 300 patients were randomly assigned to hepatectomy alone (149 patients) or hepatectomy followed by chemotherapy (151 patients). At the third interim analysis of phase III with median follow-up of 53.6 months, the trial was terminated early according to the protocol because DFS was significantly longer in patients treated with hepatectomy followed by chemotherapy. With median follow-up of 59.2 months, the updated 5-year DFS was 38.7% (95% CI, 30.4 to 46.8) for hepatectomy alone compared with 49.8% (95% CI, 41.0 to 58.0) for chemotherapy (hazard ratio, 0.67; 95% CI, 0.50 to 0.92; one-sided $P = .006$). However, the updated 5-year overall survival (OS) was 83.1% (95% CI, 74.9 to 88.9) with hepatectomy alone and 71.2% (95% CI, 61.7 to 78.8) with hepatectomy followed by chemotherapy. In the chemotherapy arm, the most common grade 3 or higher severe adverse event was neutropenia (50% of patients), followed by sensory neuropathy (10%) and allergic reaction (4%). One patient died of unknown cause after three courses of mFOLFOX6 administration.

CONCLUSION DFS did not correlate with OS for liver-only metastatic CRC. Adjuvant chemotherapy with mFOLFOX6 improves DFS among patients treated with hepatectomy for CRC liver metastasis. It remains unclear whether chemotherapy improves OS.



In conclusion, adjuvant chemotherapy with mFOLFOX6 improves DFS compared with hepatectomy alone but causes severe AEs in approximately half of the patients. It remains unclear whether chemotherapy improves OS.

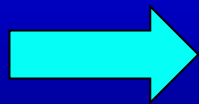
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What is the objective when treating Oligo-metastatic disease ?

Owing to the limited extension of the disease :

- Cure
- Prolonged survival
- Increase DFS and Chemotherapy-free time
- Minimally invasive and Low risk of the procedure

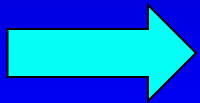


Favor Curative treatments...

Management of Oligo-Progressive Colorectal Liver Metastases

1. Is chemotherapy always indicated for OMD ?
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What is the best treatment of Oligo-metastatic disease ?

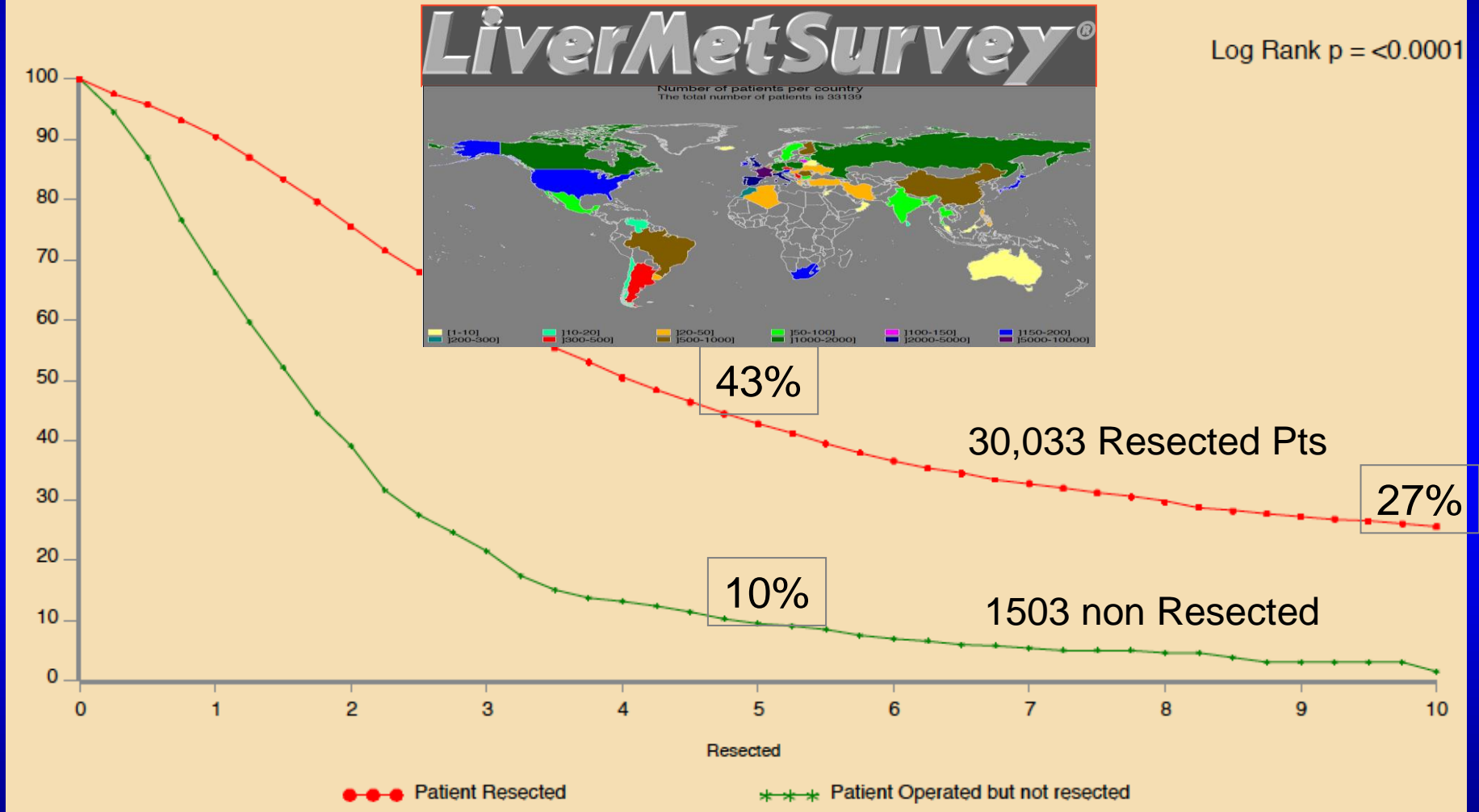


For patients with resectable OMD, **surgery remains the standard** and best (potentially) curative treatment approach.
ESMO recommendations 2022 (Cervantes et al, Ann Oncol 2022)

LIVERMETSURVEY : SURVIVAL AFTER LIVER RESECTION

Dec 2023: 31,536 Pts - 374 Centers - 64 countries

Patient Survival after a 1st liver operation for Colorectal Metastases : 28895 patients



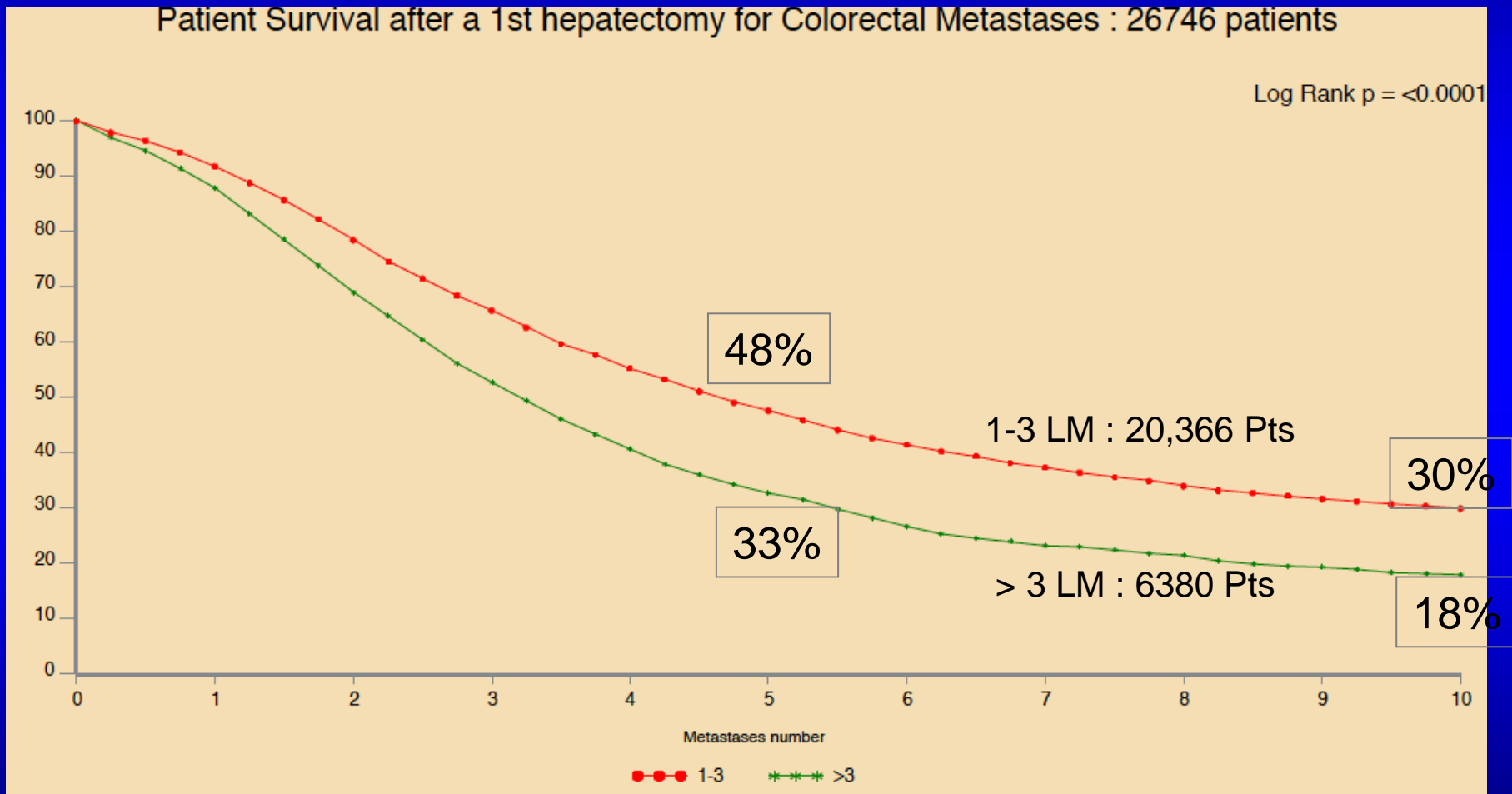
www.livermetsurvey-arcad.org

LIVERMETSURVEY : SURVIVAL AFTER LIVER RESECTION

Dec 2023: 31,536 Pts - 374 Centers - 64 countries



Patient Survival after a 1st hepatectomy for Colorectal Metastases : 26746 patients



www.livermetsurvey-arcad.org

Resection of Breast Cancer Liver Metastases

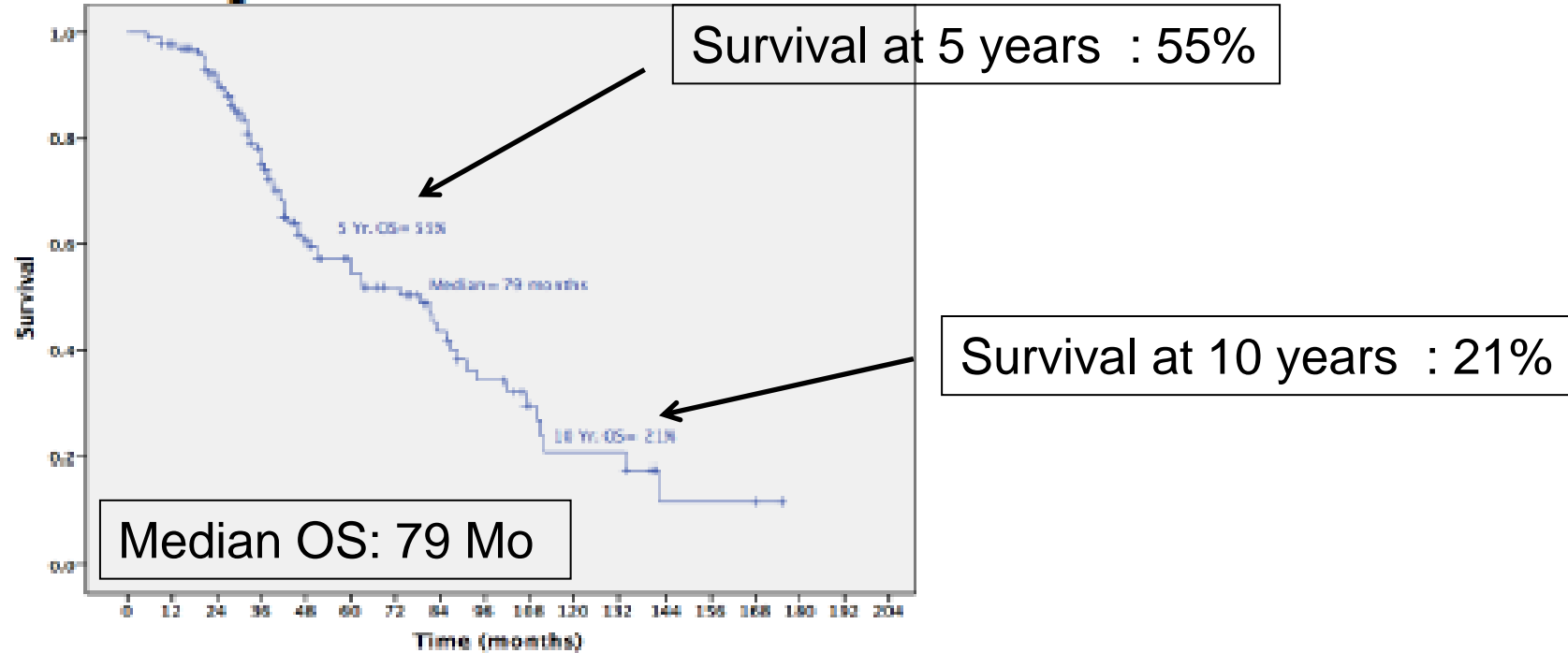
AUTHOR	DATE	Period	No	Median (mo)	3-yr Survival (%)	5-yr Survival (%)
Pocard	2000	1988-1997	52	42	49	NR
Elias	2003	1986-2000	54	34	50	34
Adam	2006	1984-2004	85	32	NR	37
Adam	2006	1983-2004	454	45	NR	41
Hoffmann	2010	1999-2008	41	58	68	48
Abbot	2012	1997-2010	86	57	NR	44
Groeschl	2012	1990-2009	115	52	52	27
Mariani	2013	1988-2007	51	91	NR	NR
Hoffmann	2015	2001-2012	42	63	NR	53
Sadot	2016	1991-2014	69	50	NR	38

5y OS: 27 – 53%
Median: 41 – 115mo

Survival after Resection of BLM

Paul Brousse Hospital - 139 Pts (1985-2012)

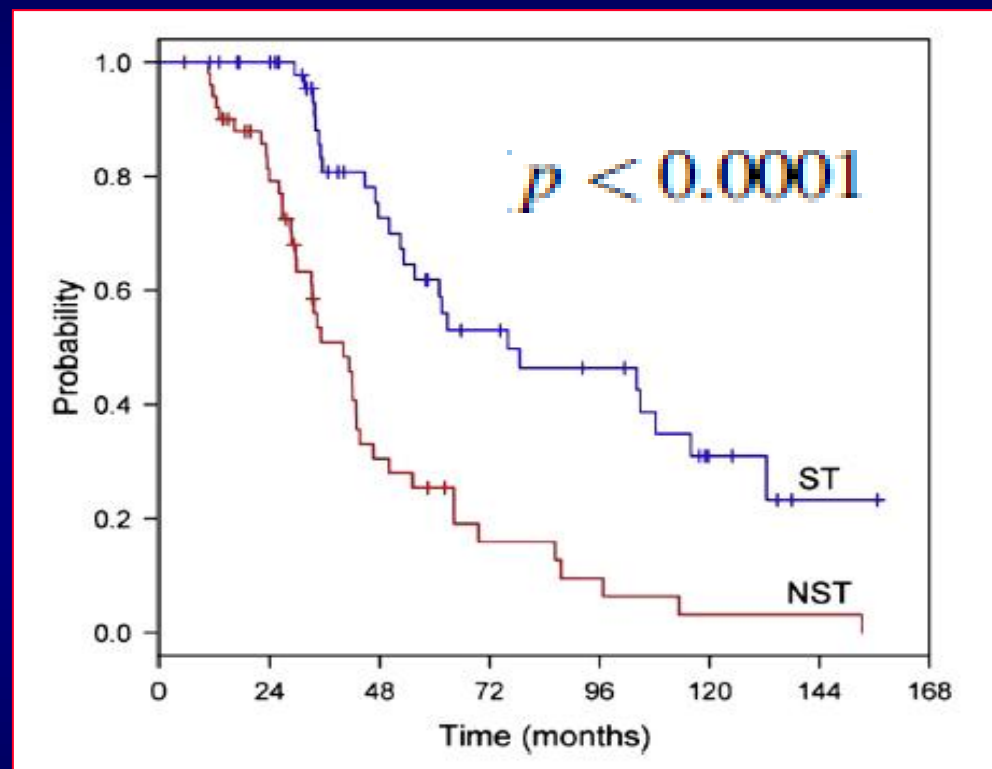
B. Since diagnosis



	Total	3 years	5 years	10 years	Median (months)
Number exposed to risk	137	76	43	7	79

Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients

P. Mariani et al. / EJSO 39 (2013) 1377–1383



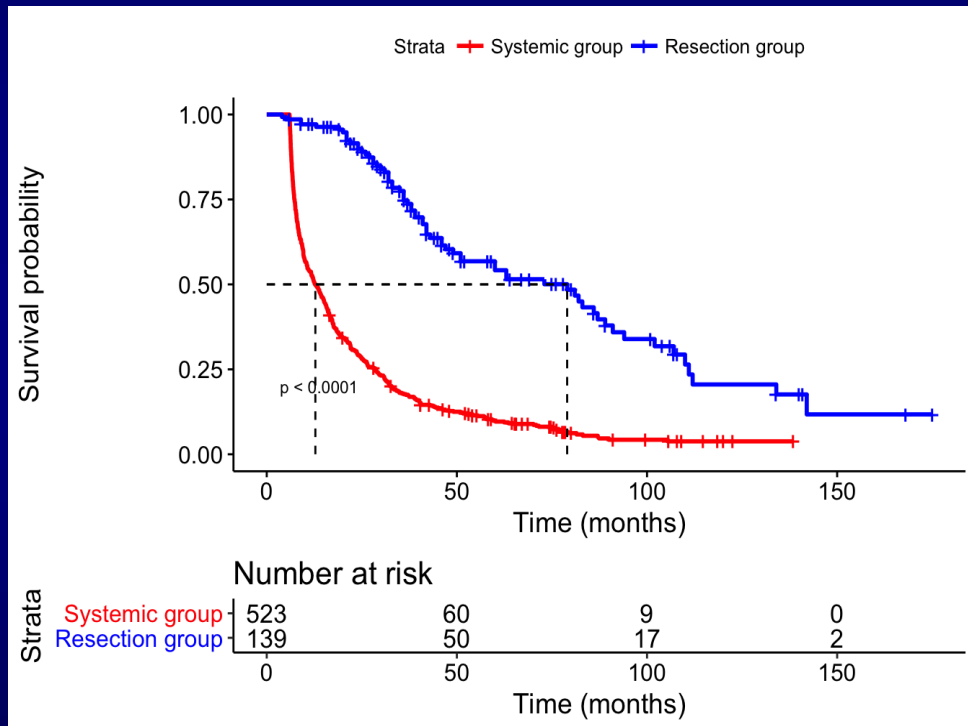
RR = 3.04-fold higher risk of death (CI: 1.87–4.92) ($p < 0.0001$) when surgery was not performed (Fig. 2), and RR = 2.324-fold higher risk of death (CI: 1.229–4.395) ($p = 0.009$) if the patients had bone metastases.

Figure 2. Comparison of survival according to liver surgery. A statistically significant difference was demonstrated using the log-rank test ($p < 0.0001$).

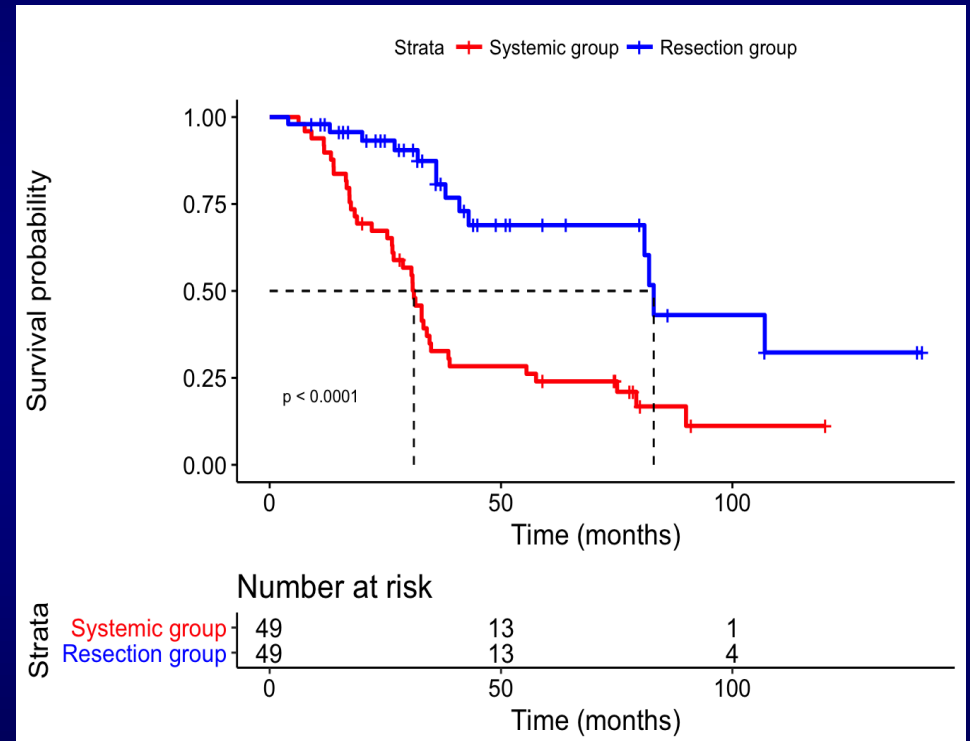
Surgical Resection versus Systemic therapy for Breast Cancer Liver Metastases. Results of a case matched comparison

A.Ruiz... R Adam (Eur J Cancer 2018)

Unmatched

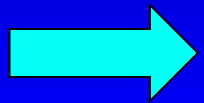


Matched

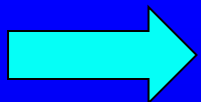


Surgery combined to systemic treatment does better than sytemic treatment alone

What is the best treatment of Oligo-metastatic disease ?



For patients with resectable OMD, surgery remains the standard and best (potentially) curative treatment approach.



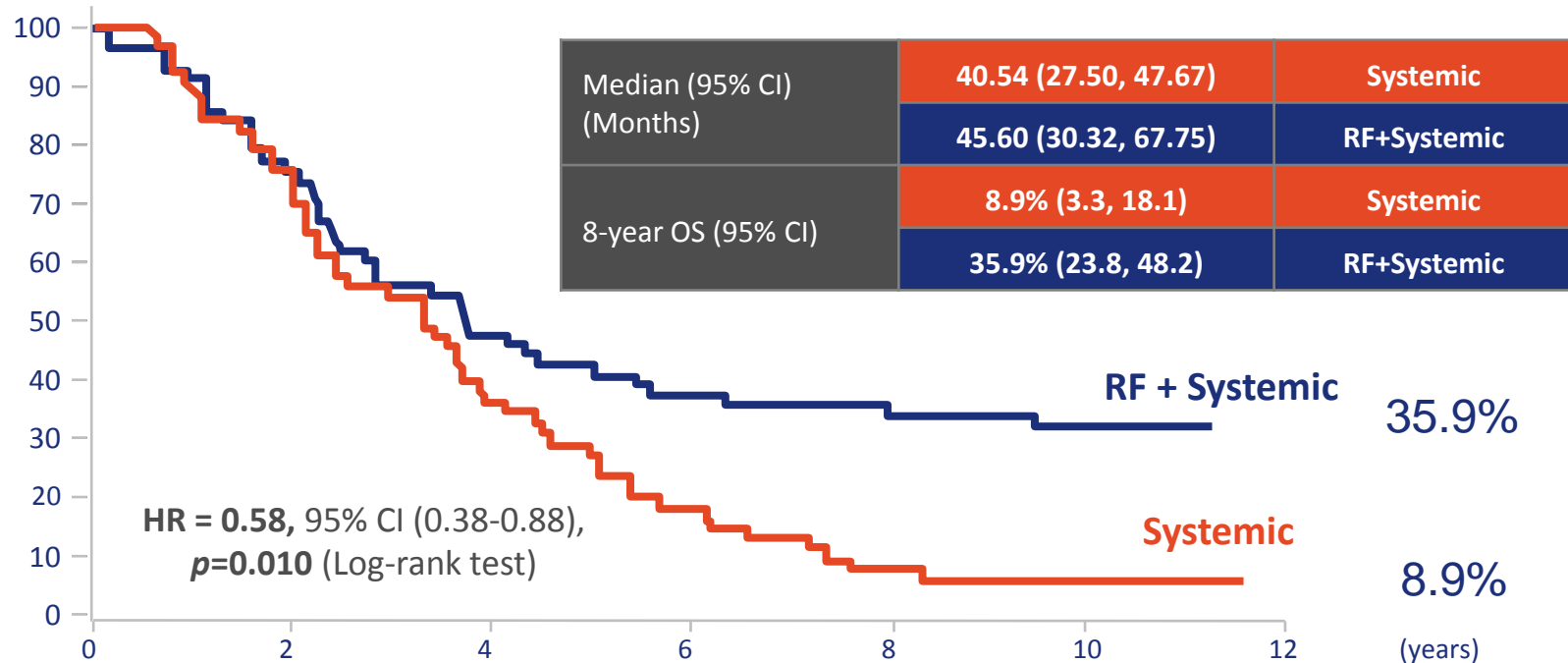
Thermal ablation such as radiofrequency ablation (RFA) has a limitation inherent to size range of **max 2-3 cm**. Safety margin of ablation is a strong predictor of complete eradication. In the randomized phase II **CLOCC trial** (ChT plus RFA \pm surgical resection versus ChT alone - median of four CRLMs -, an improvement in PFS and in OS was reported (*Ruers et al; Ann Oncol 2012*)

- Phase II EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC, Ann Oncol 2012) results at long term (10 yrs)



CLOCC : Results

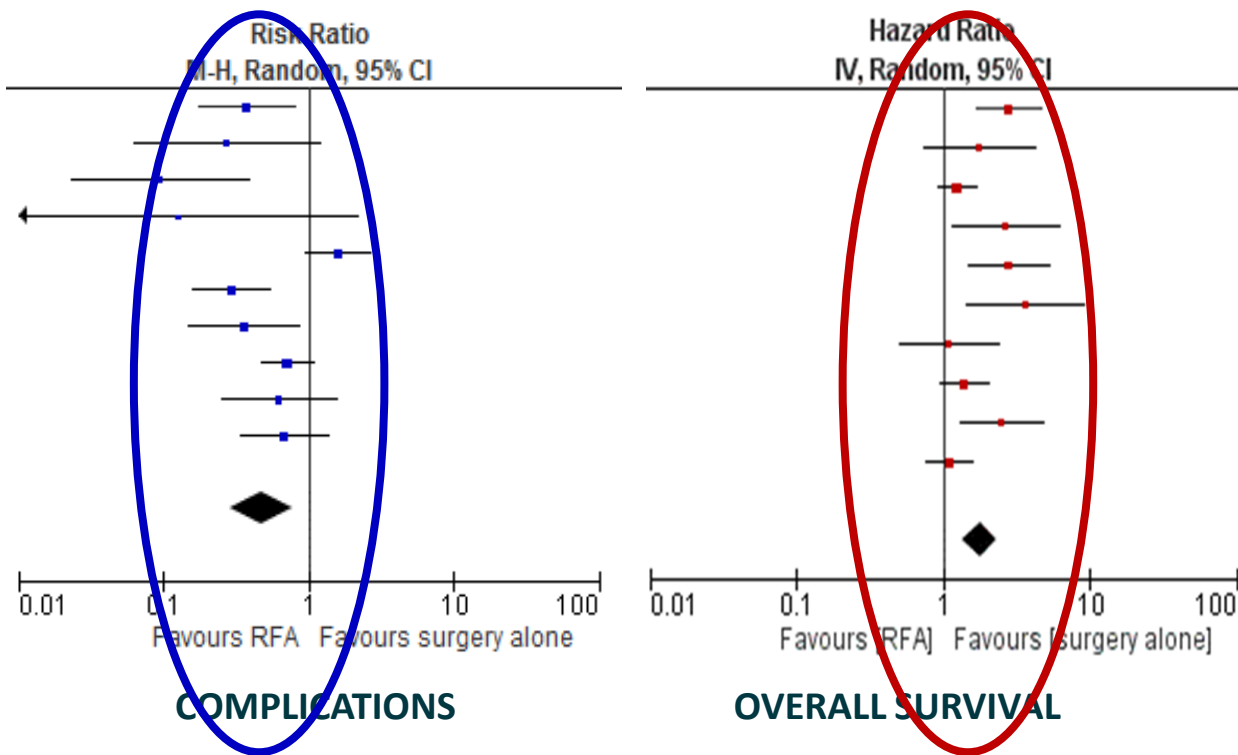
Overall Survival



O	N	Nombre de patients à risque :						Treatment
53	59	43	21	11	4	2	— Systemic	
39	60	44	28	21	19	9	— RF + Systemic	

SURGERY VERSUS ABLATION

COMPLICATIONS & OVERALL SURVIVAL



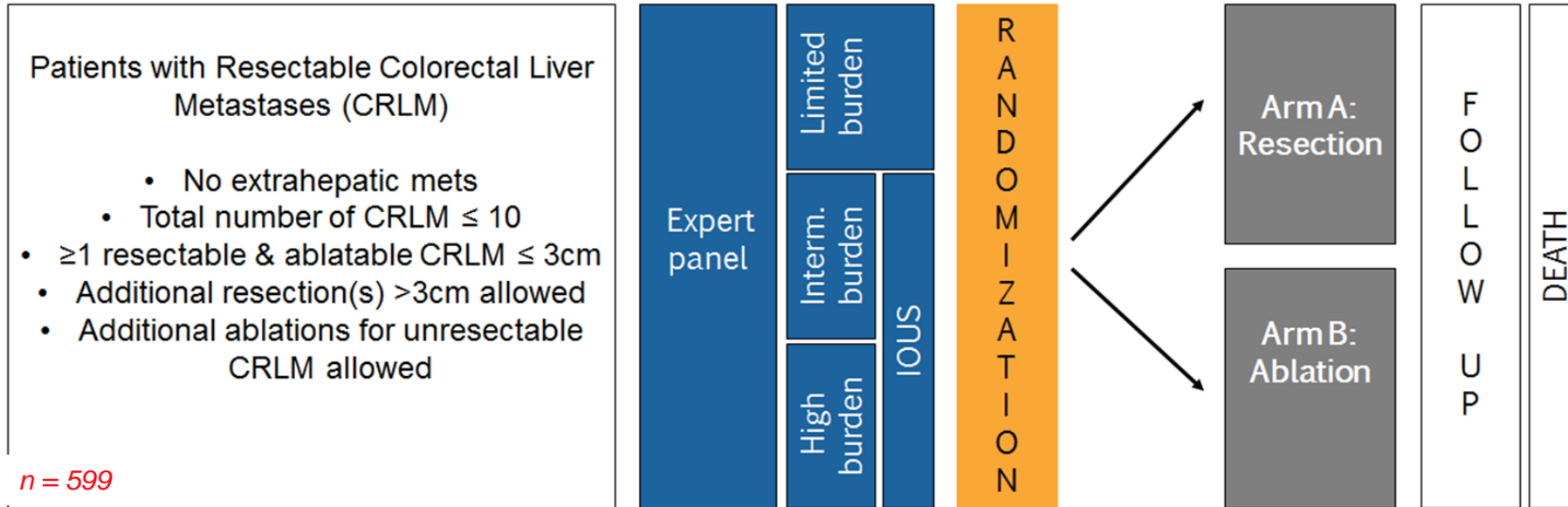
Cardiovasc Intervent Radiol (2018) 41:1189–1204
<https://doi.org/10.1007/s00270-018-1959-3>

Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis

Martijn R. Meijerink¹ · Robbert S. Puijk¹ · Aukje A. J. M. van Tilborg¹ · Kirsten Holdt Henningsen² · Llenalia Garcia Fernandez² · Mattias Neyt² · Juanita Heymans³ · Jacqueline S. Frankema³ · Koert P. de Jong⁴ · Dick J. Richel⁵ · Warner Prevoo⁶ · Joan Vlayen²

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Abdalla 2004	1.026	0.2588	11.5%	2.79 [1.68, 4.63]
Gleisner 2008	0.571	0.4381	6.6%	1.77 [0.75, 4.18]
Berber 2008	0.2151	0.1579	15.3%	1.24 [0.91, 1.69]
Hur 2009	0.9746	0.4304	6.7%	2.65 [1.14, 6.16]
McKay 2009	1.0217	0.3261	9.3%	2.78 [1.47, 5.26]
Lee KH 2012	1.2845	0.4758	5.9%	3.61 [1.42, 9.18]
Aliyev 2013	0.0953	0.4023	7.3%	1.10 [0.50, 2.42]
Agcaoglu 2013	0.3365	0.1923	14.0%	1.40 [0.96, 2.04]
Jasarovic 2014	0.9163	0.3336	9.1%	2.50 [1.30, 4.81]
Hof 2016	0.0953	0.1817	14.4%	1.10 [0.77, 1.57]
Total (95% CI)			100.0%	1.78 [1.35, 2.33]
Heterogeneity: Tau ² = 0.10; Chi ² = 21.77, df = 9 (P = 0.010); I ² = 59%				
Test for overall effect: Z = 4.15 (P < 0.0001)				

Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)



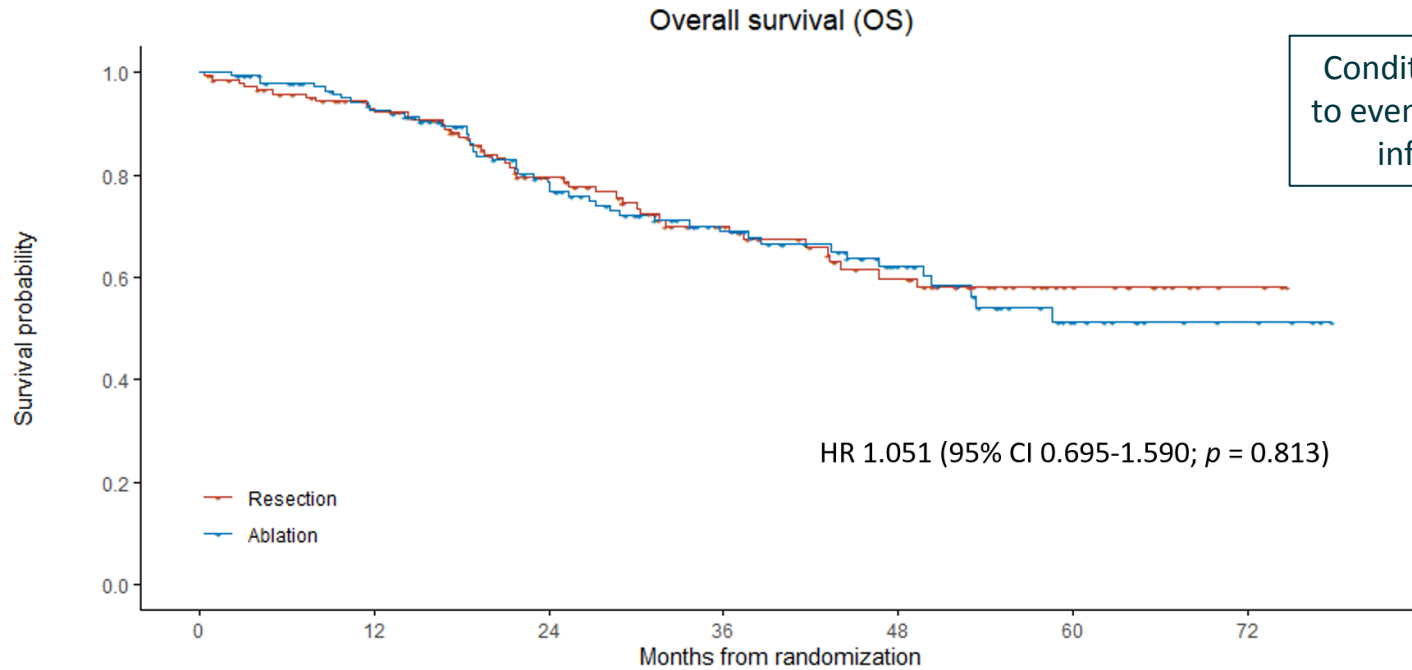
Phase III multicenter partially single-blind randomized controlled trial to prove/disprove non-inferiority of thermal ablation compared to partial hepatectomy for small resectable colorectal liver metastases

- Approach (percutaneous, laparoscopic or open) according to local expertise
- If limited disease burden (max 3 CRLM ≤ 3 cm) consider percutaneous / laparoscopic approach
- If intermediate or high disease burden randomize after eligibility check (after IOUS) during OR (single-blind)

- 62% low disease burden - 22% chemo first
- **Median number CRLM = 2**
- **Mean-size CRLM 14 mm**
- *64% of resections in low disease burden group performed using (robot) laparoscopy*
- *83% of ablations in low disease burden group performed percutaneously*

RESULTS

OVERALL SURVIVAL – PRIMARY ENDPOINT



Conditional probability to eventually prove non-inferiority 91%!

Number at risk (number of events)

	0	12	24	36	48	60	72
Strata Resection	148 (0)	124 (10)	84 (26)	54 (35)	37 (42)	15 (43)	3 (43)
Ablation	148 (0)	124 (10)	89 (27)	61 (37)	36 (42)	15 (47)	5 (47)

Months from randomization

SUMMARY

- **COLLISION stopped at halftime based on predefined stopping rules for**
 - Showing benefit of the experimental arm (ablation) over standard-of-care (resection)
- **For patients with small-size colorectal liver metastases, thermal ablation compared to standard-of-care surgical resection**
 - Substantially reduced morbidity and mortality
 - treatment related mortality 2.1% (resection) → 0.0% (ablation)
 - all-cause 90-day mortality 2.1% (resection) → 0.7% (ablation)
 - AEs rate 56% (resection) → 19% (ablation) and SAE rate 20% (resection) → 7% (ablation)
 - Was at least as good as surgical resection in locally controlling CRLM
 - no difference in *per-patient* local control: HR 0.131 (95% CI 0.016-1.064; p = 0.057)
 - superior *per-tumor* local control: HR 0.092 (95% CI 0.011-0.735; p = 0.024)
 - Showed no difference in local & distant tumor progression-free survival
 - Did not compromise overall survival (OS)

Comments

- COLLISION was addressed to **limited** (median 2), **small** size (13mm) and **ultrasound visible** CRLM
- Specific comparison of each Tt : only for **limited disease burden** ($< 3, \leq 3\text{cm}$)
- For intermediate and high tumor burden \rightarrow IOUS during OR
- In **18%** of the cases, thermal ablation was **associated to surgical resection**



Equal results with less risk for a very limited subset of patients

The evolving role of radiation therapy as treatment for liver metastases



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc



K. Arabiah, G. Liao, Q. Shen et al. 2022

Summary of some selected prospective stereotactic body radiotherapy series.

Study	Design	Case and lesions	Dose (Gy) /fractions	Follow-up	Local control	Overall survival	PFS	Toxicity
Hoyer M 2006	Phase II	64 patients 141 lesions	45/3	4.3 (0.2-6.3) years	1-year: 86%	1-year: 67% 5-year: 13%	Median: 6.5 Mo 2-year: 19%	Grade 2: 48%
Kavanagh B 2006	Phase III	21 patients	60/3	19 (6-29) Mo	Median: 18 Mo 1-year: 93%	NA	NA	Grade 3: 1
Rusthoven K 2009	Phase I/II	47 patients 63 lesions	36-60/3	16 (6-54) Mo	1-year: 95% 2-year: 92%	Median: 20.5 Mo 2-year: 30%	NA	Grade 3: 2%
Lee M 2009	Phase I	68 patients	54-60/6	10.8 Mo	1-year: 71%	Median: 17.6 Mo 1-year: 63%	NA	Grade 3: 10%
Rule W 2011	Phase I	27 patients 37 lesions	30-60/5	20 (4-53) Mo	1-year: 72%	Median: 37 Mo 2-year: 57.6%	NA	Grade 3: 1
Scorsetti M 2012	Phase II	61 patients 76 lesions	75/3	6.1 years	1-year: 95%	Median: 27.6 Mo 1-year: 85% 5-year: 18%	Median: 12 Mo	No grade 3
Hong T 2017	Phase II	89 patients 143 lesions	40 GyE/5	30.1 (14.7-53.8) Mo	1-year: 71.9% 3-year: 61.2%	1-year: 66.3% 2-year: 35.9% 3-year: 20.8%	NA	No Grade ≥ 3
Folkert M 2021	Phase I	33 patients 39 lesions	35-40/1	25.9 Mo	4-year: 96.6%	2-year: 82%	NA	No Grade ≥ 3

Abbreviations: Mo, months; NA, not available; PFS, progression-free survival.

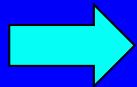
No randomised and No large prospective trials...A treatment option for inoperable pts

Management of Oligo-Progressive Colorectal Liver Metastases

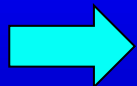
1. Is chemotherapy always indicated for OMD ?
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What definition for oligo progressive disease ?

- Appearance of liver metastases in a context of CRC ?
- Progression of liver metastases in place ?



Synchronous : even for limited disease → Short chemotherapy first to have the « test of time » and one or two stage surgery (Liver + Colon) in case of tumor control by chemotherapy (*Expert Consensus, Adam et al, Cancer treatment Reviews 2015*)



Metachronous : depends on timing, adjuvant chemotherapy received and aggressiveness of recurrence

- Early recurrence (< 6 months): Chemotherapy and surgery
- Late recurrence (> 6 months) : Surgery upfront for easy-to-resect LM

What definition for progressive disease ?

- Appearance of liver metastases in a context of CRC ?
- **Progression of liver metastases in place ?**

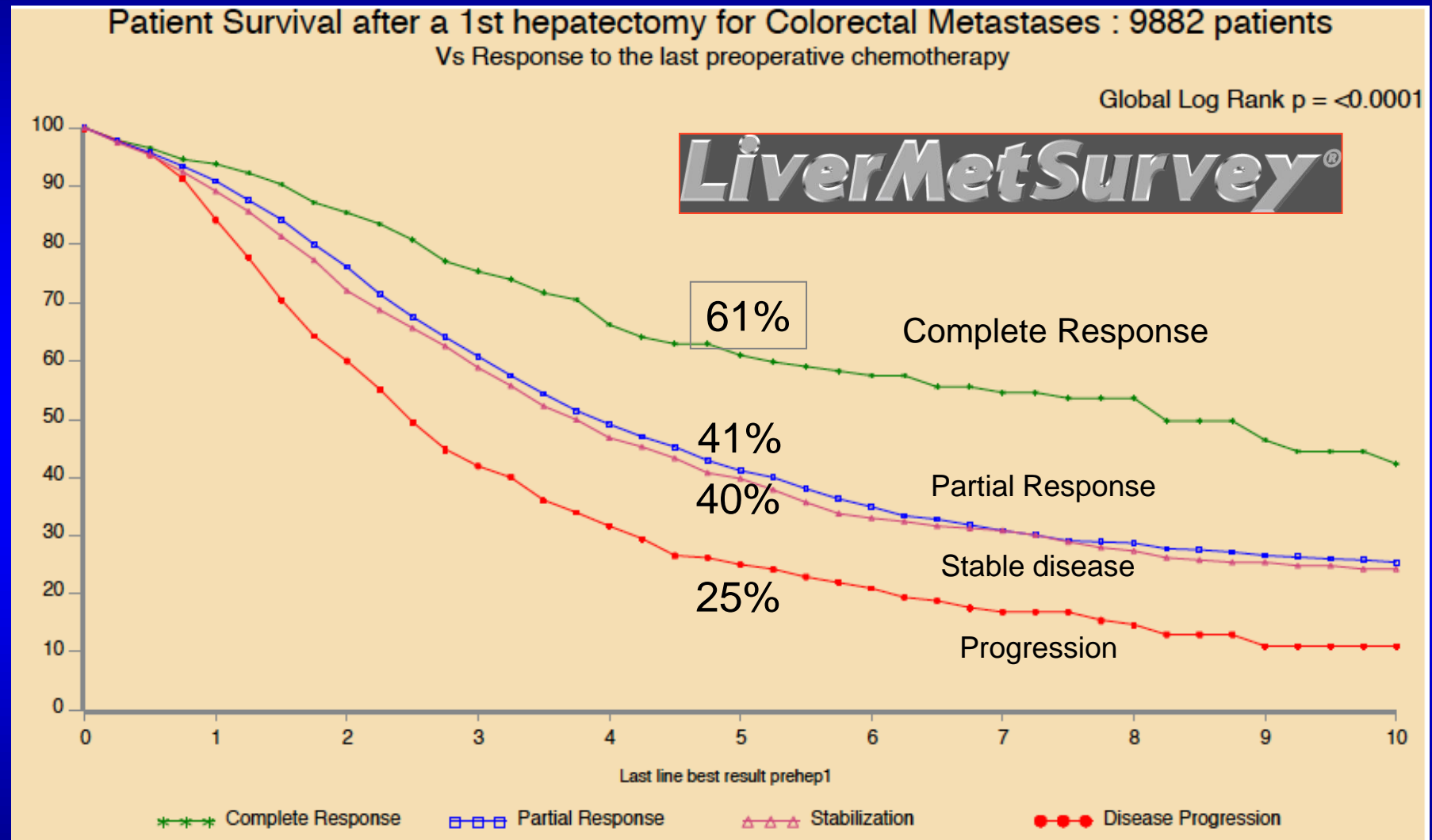
➡ Relative contraindication to surgery because poor long-term outcome

➡ Control of the disease by chemotherapy, even with a 2nd line regimen and then surgery...

➡ Exception : progression despite optimal therapy and unlikely to obtain a response... Surgery at some conditions ?
if complete and consensus MDT decision

LIVERMETSURVEY : Overall Survival after Liver resection

June 2020: 28,081 Pts - 366 Centers - 63 countries



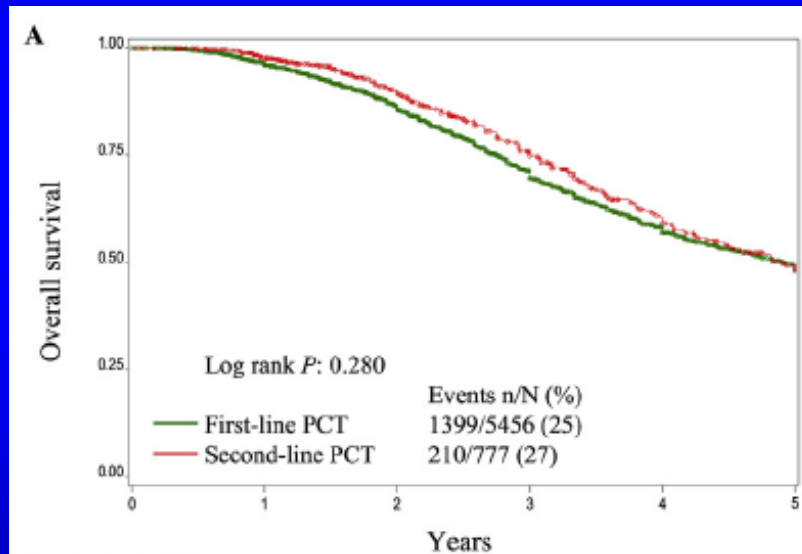
www.livermetsurvey-arcad.org

Resection of colorectal liver metastases after second-line chemotherapy: is it worthwhile? A LiverMetSurvey analysis of 6415 patients

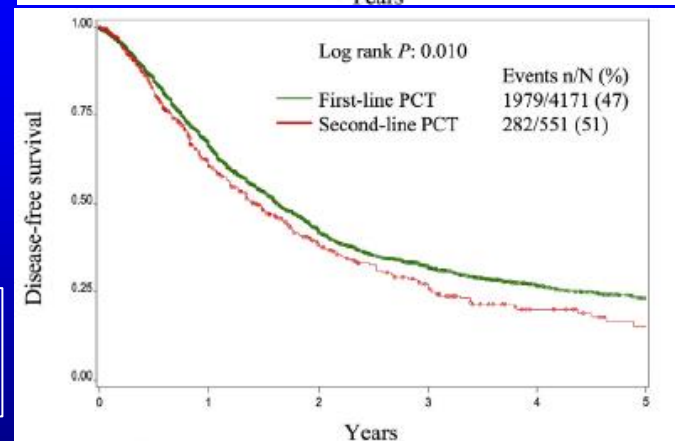
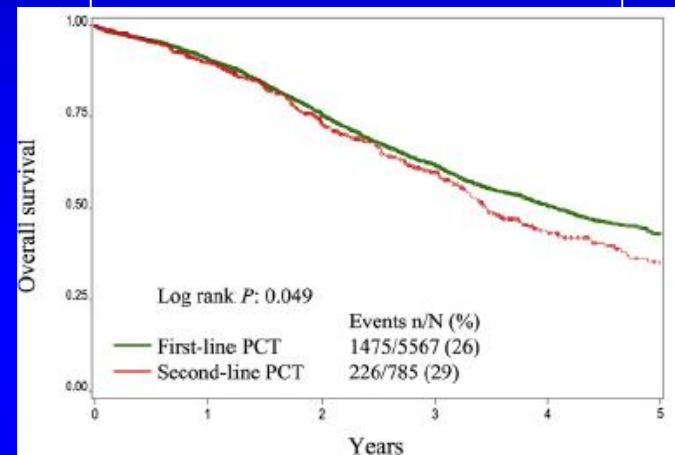


R. Adam et al. / *European Journal of Cancer* 78 (2017)

Survival after Diagnosis



Survival after Hepatectomy



Surgery should not be denied after the failure Of 1st line chemotherapy

Progression while Receiving Preoperative Chemotherapy Should Not Be an Absolute Contraindication to Liver Resection for Colorectal Metastases

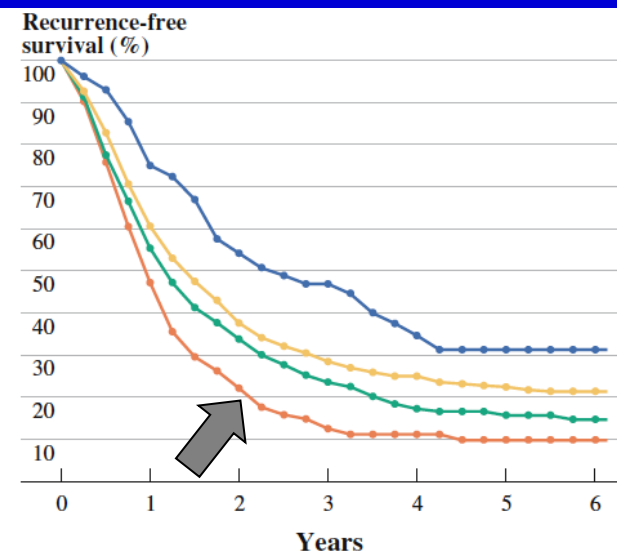
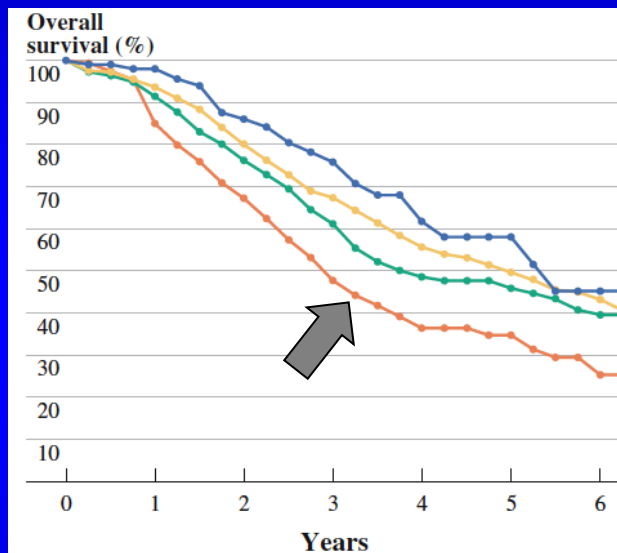
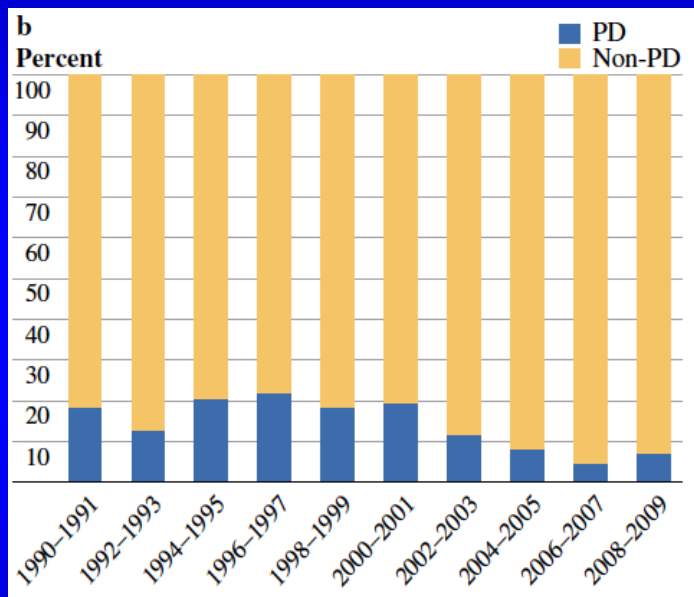
L. Viganò et al.

Ann Surg Oncol (2012)

Annals of

SURGICAL ONCOLOGY

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last line response: — Complete response — Partial response — No change — Disease progression

No. of factors	>3 metastases	Size \geq 50 mm	CEA \geq 200 ng/mL ^a	Survival	
				3 years (%)	5 years (%)
0	0	0	0	60.5	53.3
1	1	0	0	38.2	29.9
	0	1	0	26.7	19.1
	0	0	1	7.9	4.1
	1	1	0	8.0	4.2
2	1	0	1	0.8	0.2
	0	1	1	0.1	0
	1	1	1	0	0

Liver resection is contraindicated only in patients with >3 and large (\geq 5 cm) metastases, or whenever the CEA value is \geq 200 ng/mL, for whom further chemotherapy is recommended.

Management of Oligo-Progressive Colorectal Liver Metastases

1. Is chemotherapy always indicated for OMD ?
2. What are the objectives ?
3. What is the best treatment ?
4. What impact of progression on the management
5. Take-Home messages

Take Home messages

1. Definition of OMD is heterogeneous but means limited disease ...
2. Neo adjuvant Chemo is usually indicated unless very limited CRLM but no evidence-based data supporting the real benefit of periop chemo on OS in resectable disease
3. Main objective is cure or prolonged survival...
4. Surgery remains the standard of care with 40-50% OS at 5 and 25-30% at 10 years and a potential of cure...
5. Thermo ablation could achieve equivalent results for small CRLM
6. Other treatments (SBRT, TACE, TARE...) are not ranged as curative...
7. Tumor Progression usually requires neo adjuvant chemotherapy before any local treatment to optimize outcome