Memorial Sloan Kettering Cancer Center

CRC Oligometastatic disease

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Disclosures

- **Research Support:**

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  R21 CA128391-02
  R01 CA240569-01

- Industry:

SIRTEX Medical Inc: Phase I Trial Y90 Post HAI: Clinical CRC 2013

Angiodynamics/ Neuwave/ SOTA Medical/ HS Medical/ Perseon

BTG: EPOCH Trial

- Consultant, Advisory Boards:

- J&J/ Ethicon
- Terumo
- BTG/Boston Scientific
- SIRTEX
- Varian

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Oligometastatic colorectal cancer: prognosis, role of locoregional treatments and impact of first-line chemotherapy—a pooled analysis of TRIBE and TRIBE2 studies by Gruppo Oncologico del Nord Ovest

TRIBE and TRIBE2 are 2 phase III Randomized MCT trials

1187 initially unresectable mCRC patients, ECOG ≤ 2. Age: 71-75

OMD: Fulfilling all criteria: Up to 5 Metastases
Not more than 3 organs involved.
NO: ASCITES, Peritoneal, Bone and CNS Mets

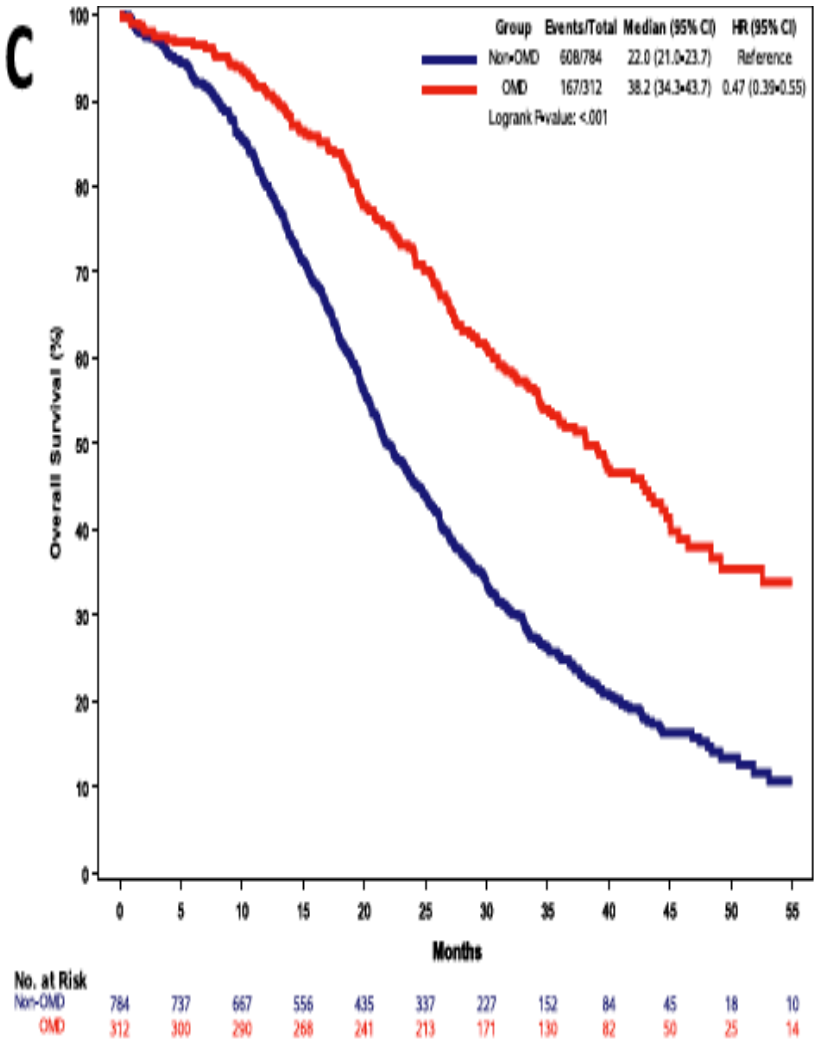
312/1187 (28%) classified OMD

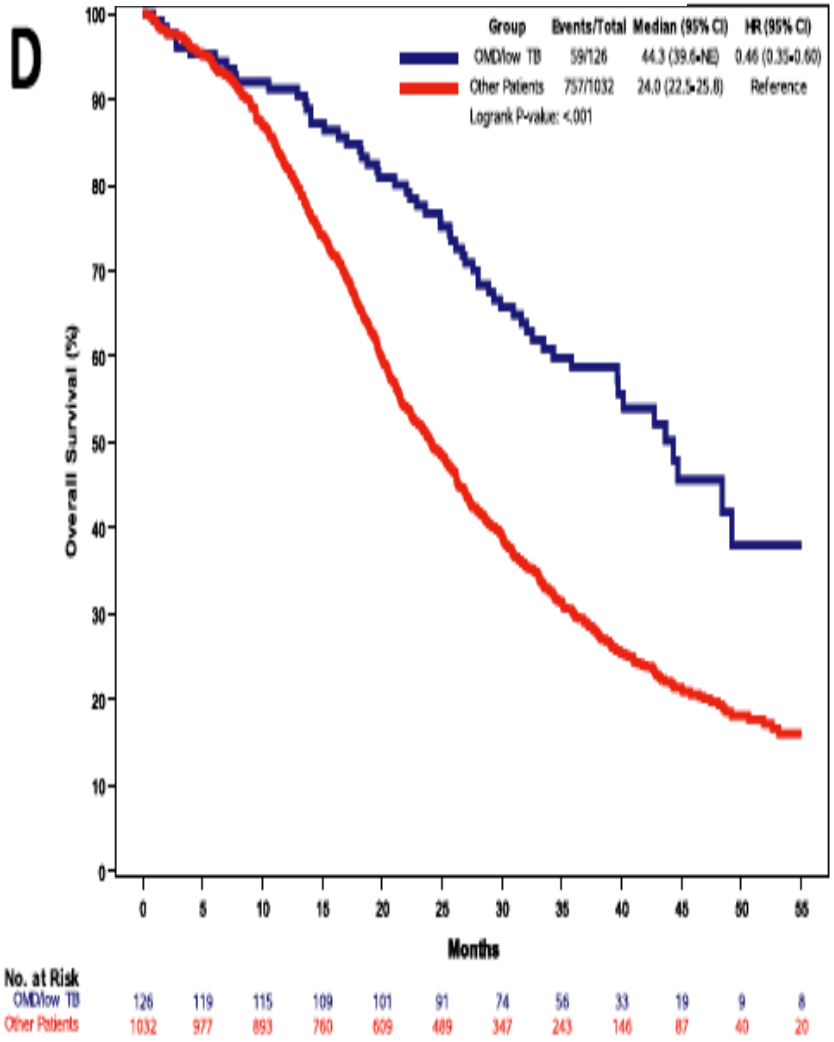
OMD: Low Tumor Burden: Up to 3/organ none over 3 cm

126/312 (40%) OMD Low TB

OS

R. Moretto et al. / European Journal of Cancer 139 (2020) 81–89





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The value of tumour debulking for patients with extensive multi-organ metastatic colorectal cancer

Elske C. Gootjes [a,1], Lotte Bakkerus [a,1], Albert J. ten Tije [a,c], Petronella O. Witteveen [d], Tineke E. Buffart [a], John A. Bridgewater [e], John N. Primrose [f], Cornelis Verhoef [b], Henk M.W. Verheul [a,*]

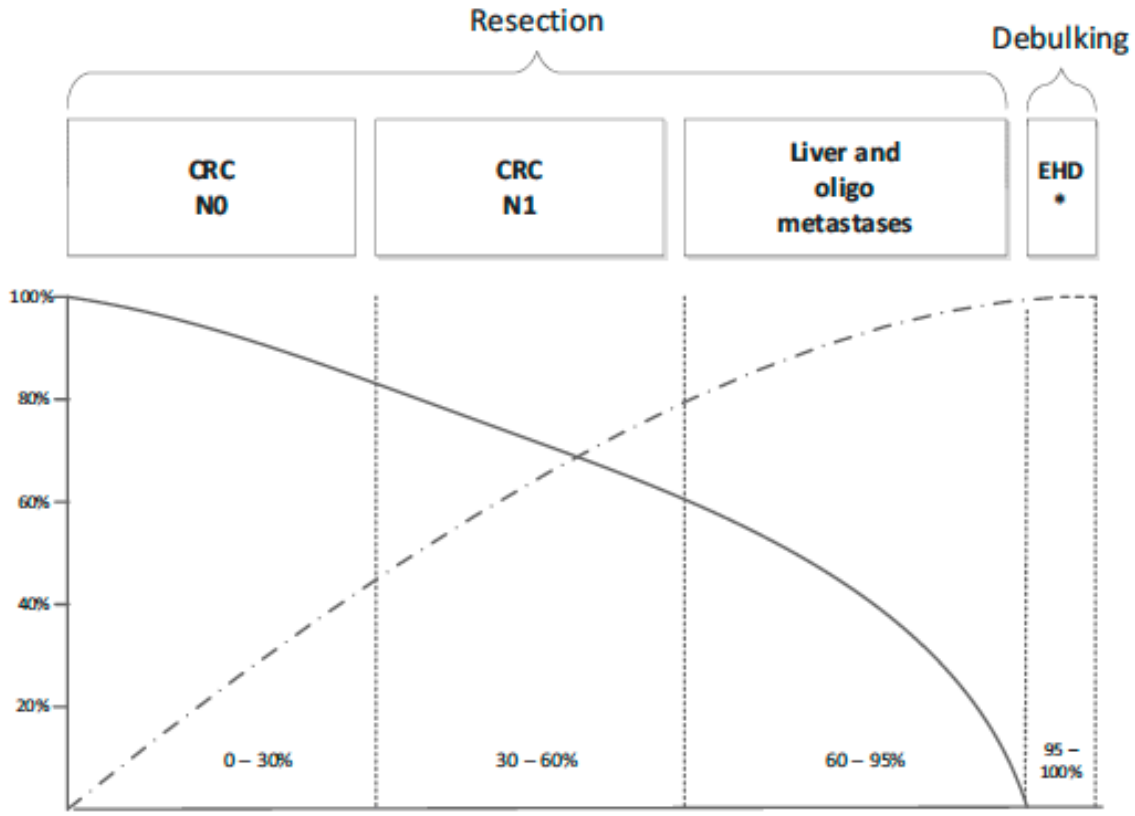

Fig. 1. Resection or debulking in CRC. Different stages of colorectal carcinoma, CRC with no positive lymph nodes (stage I and II), pathological lymph nodes present (stage III and stage IV disease), separated in liver and oligometastases and multi-organ extrahepatic disease (≥2 different organs with ≥ extrahepatic lesions). Solid line showing the chance of curability and the dashed line showing the chance of presence of micrometastases. CRC, colorectal cancer; EHD, Extrahepatic disease.

Systemic Therapy +/- RFA

CLOCC trial

SURVIVAL	Median Months	3	5	8 years	P value
Folfox	40.5	55.2	30.3%	8.9%	0.01
Folfox+RFA	45.6	56.9	43.1.%	35.9%	

Level 1 evidence

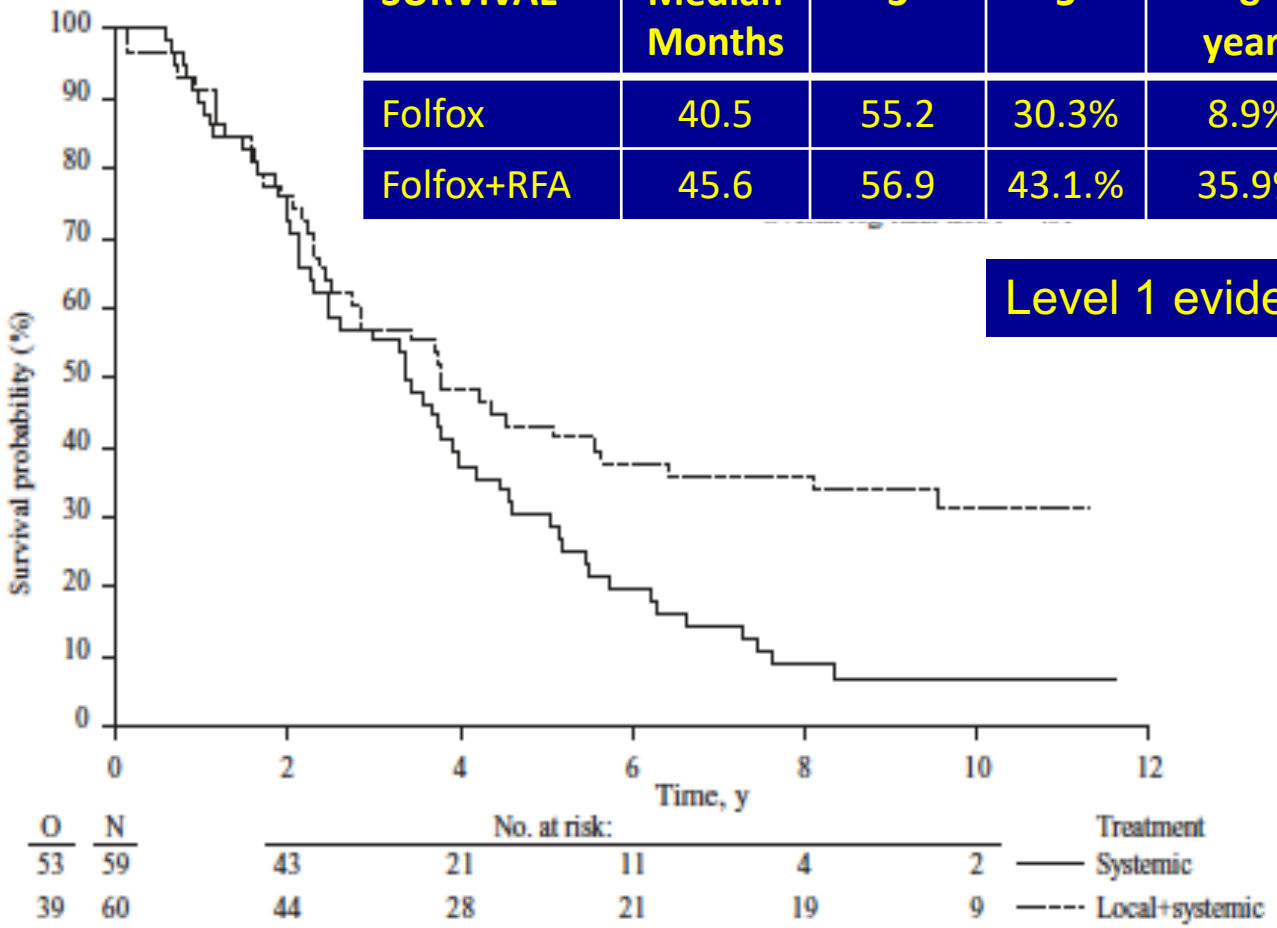

Figure 2. Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .01). P value was calculated using a two-sided log-rank test.

Ruers et al, Annals of Oncology 2012
Ruers et al ASCO 2015; JCO 33, abstract 3501
Ruers et al: JNCI Natl Cancer Inst (2017) 109 (9): djx015

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- 2002-2012: 162 patients: 233 tumors
  - (116/62, 72% post resection)

- Technique effectiveness: 94%
  - (Complete Ablation 4-6 week CT scan)

- Median LTPFS: 26 months
- 5 year Survival: 31%
- Median Survival: 36 months
- Lung Mets OS: 35 months
- More than 1 site of EHD: 14 months (HR: 1.8)

Shady W, Petre EN, Gonen M, Solomon SB, D' Angelica M, Kemeny NE, Sofocleous CT, et al, Radiology 2015

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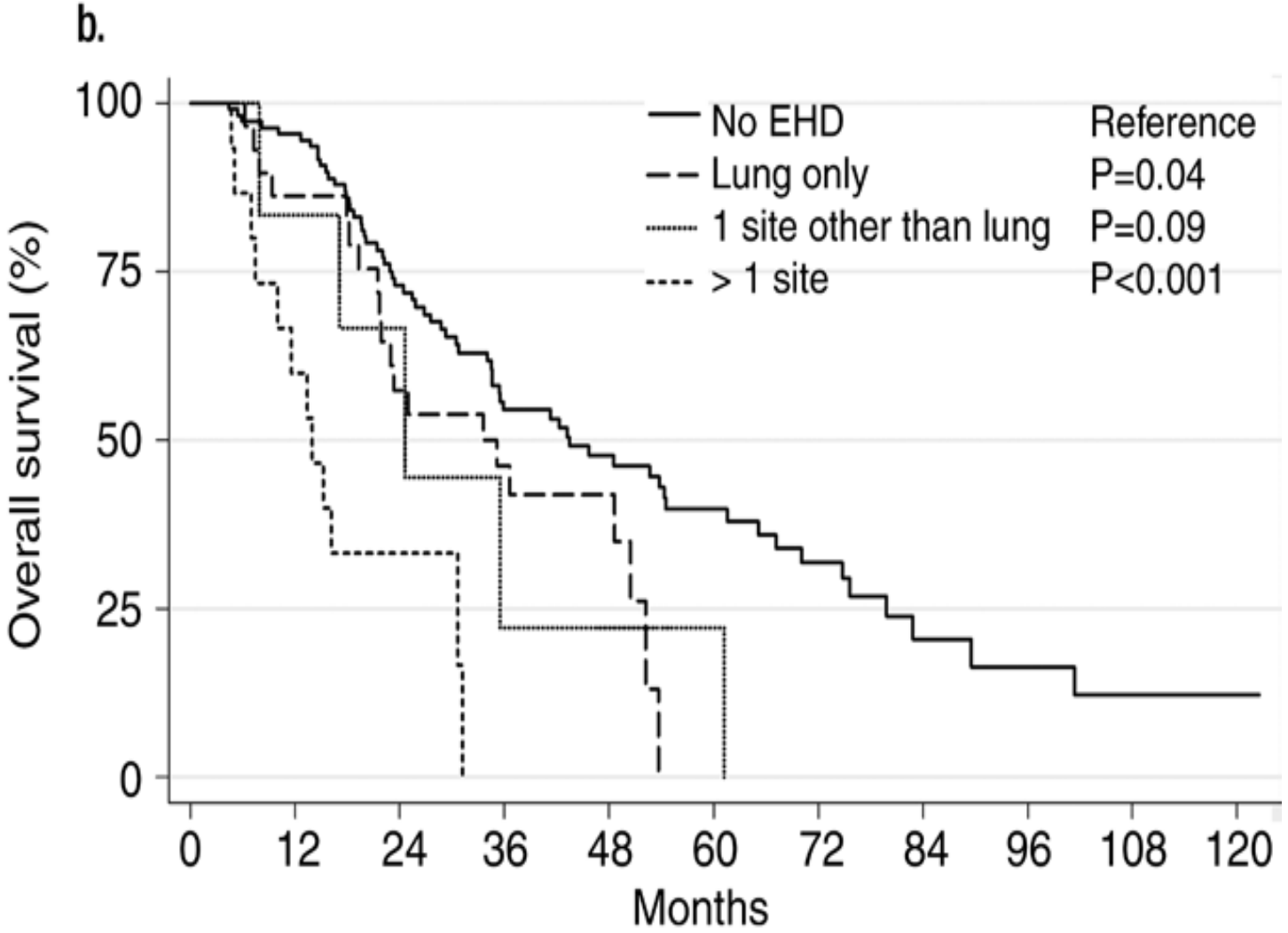
Radiology

2002-2012:
162 patients: 233 tumors

Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes—A 10-year Experience at a Single Center[1]



Shady W, Petre EN, Gonen M, Solomon SB, D' Angelica M, Kemeny NE, Sofocleous CT, et al, Radiology 2016

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Tumor Progression and Survival

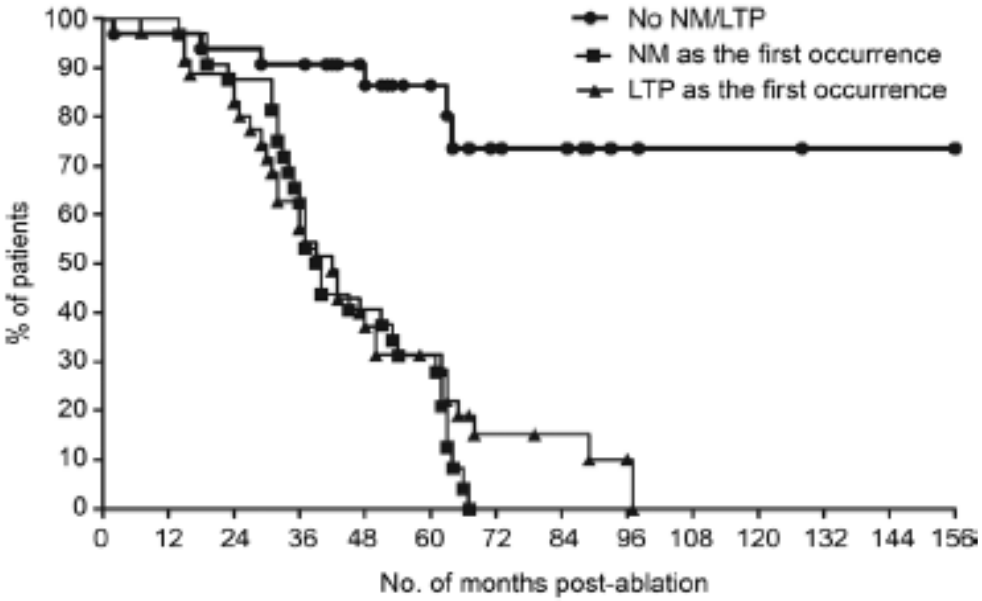

Figure 5: Kaplan-Meier curves show long-term survival in patients without NM or LTP, NM as first occurrence, and LTP as first occurrence. Best overall survival was observed in patients without either LTP or NM. No difference in overall survival was observed between patients with LTP versus those with NM remote from the treated site.

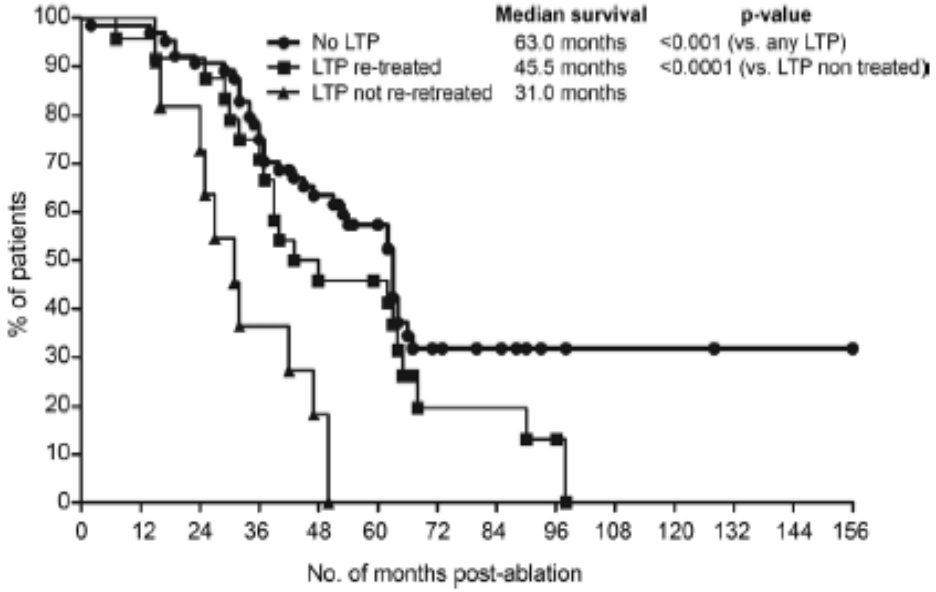

Figure 3: Kaplan-Meier curves of overall survival stratified by LTP and re-treatment. Highest survival rate was observed for patients without LTP (median survival: 63.0 months), followed by patients with LTP who underwent re-treatment (median survival: 45.5 months); lowest survival rate observed was for patients with LTP and no re-treatment (median survival 31.0 months; log-rank test for all comparisons in survival was significant at $P < .001$).

Shady W, Sofocleous CT et al: Radiology 2016

Solbiati L, et al Radiology;263(5):958-68

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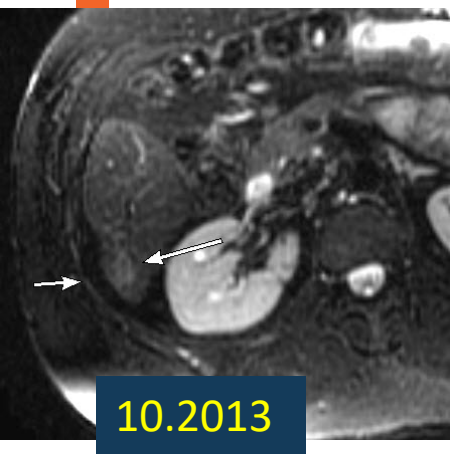
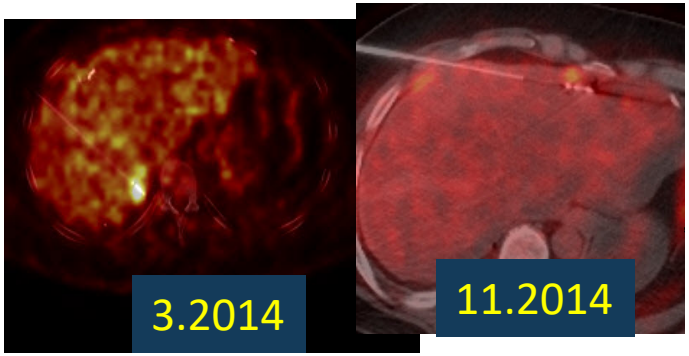
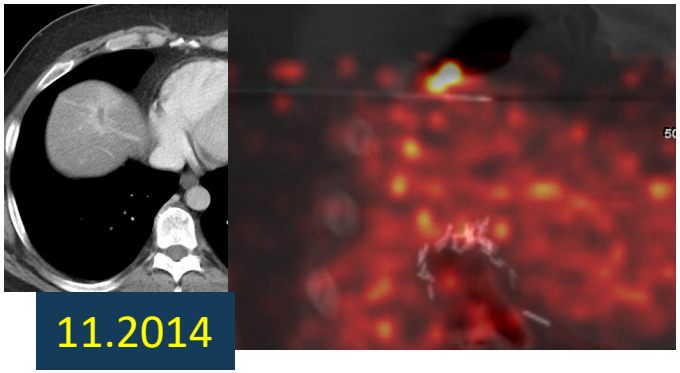
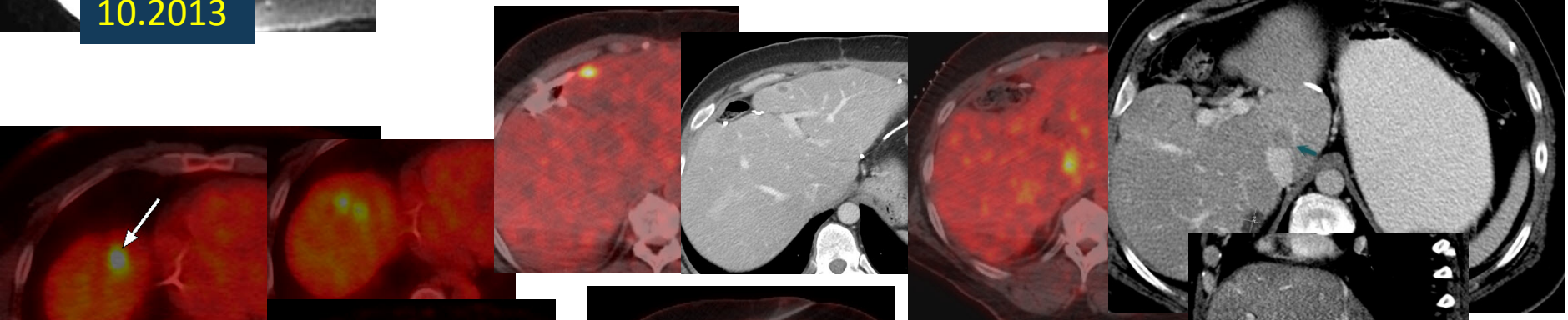
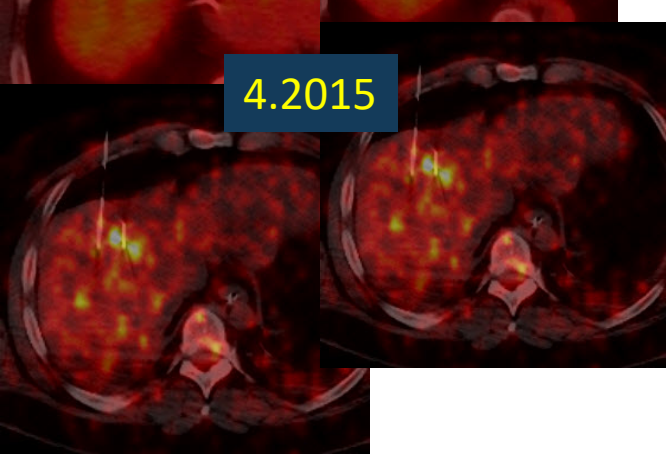
Example of of Surveillance and retreatment
39 yo male post resesction and HAIP











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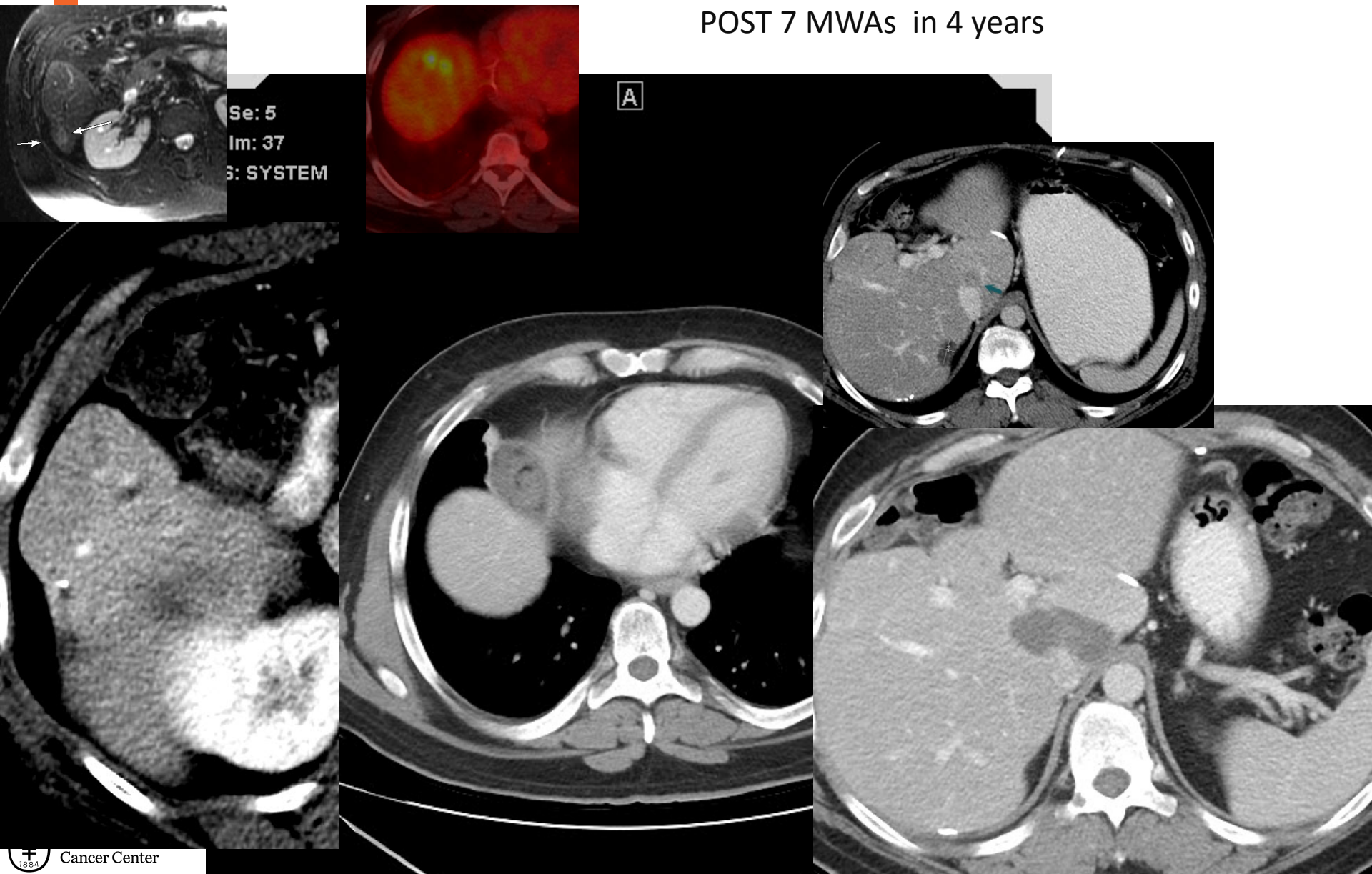
Example of of Surveillance and retreatment
39 yo male post resection and HAIP 4 years Follow-up

POST 7 MWAs in 4 years



Y90

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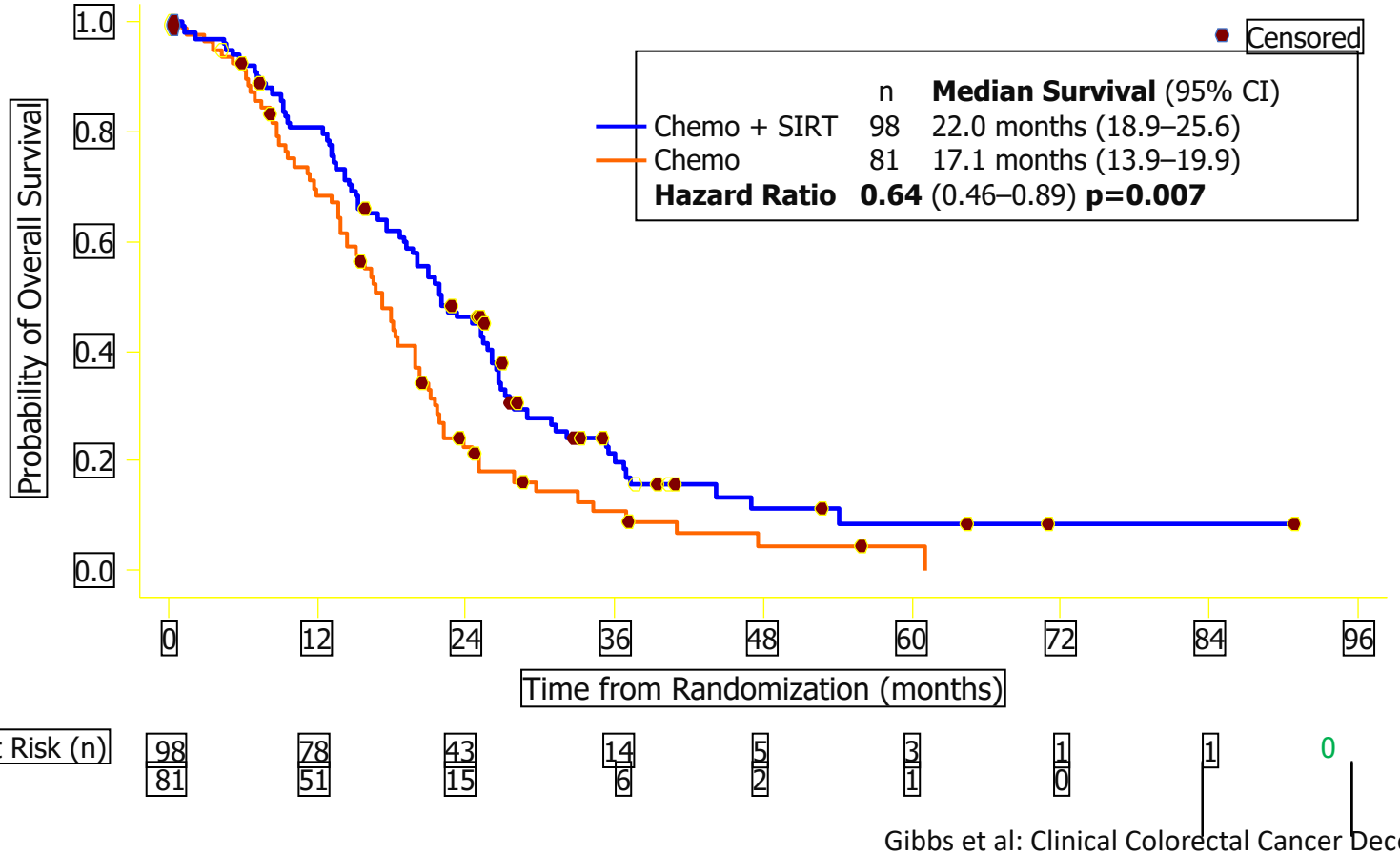
OS for RCP/ mCRC Patients with Right-Sided Primary Tumours

For the 179/739 patients (24.2%) with a RSP tumor, EHD: 39%
Improved OS in SIRT group(median, 22.0 vs. 17.1 months HR, 0.641; P: .008).

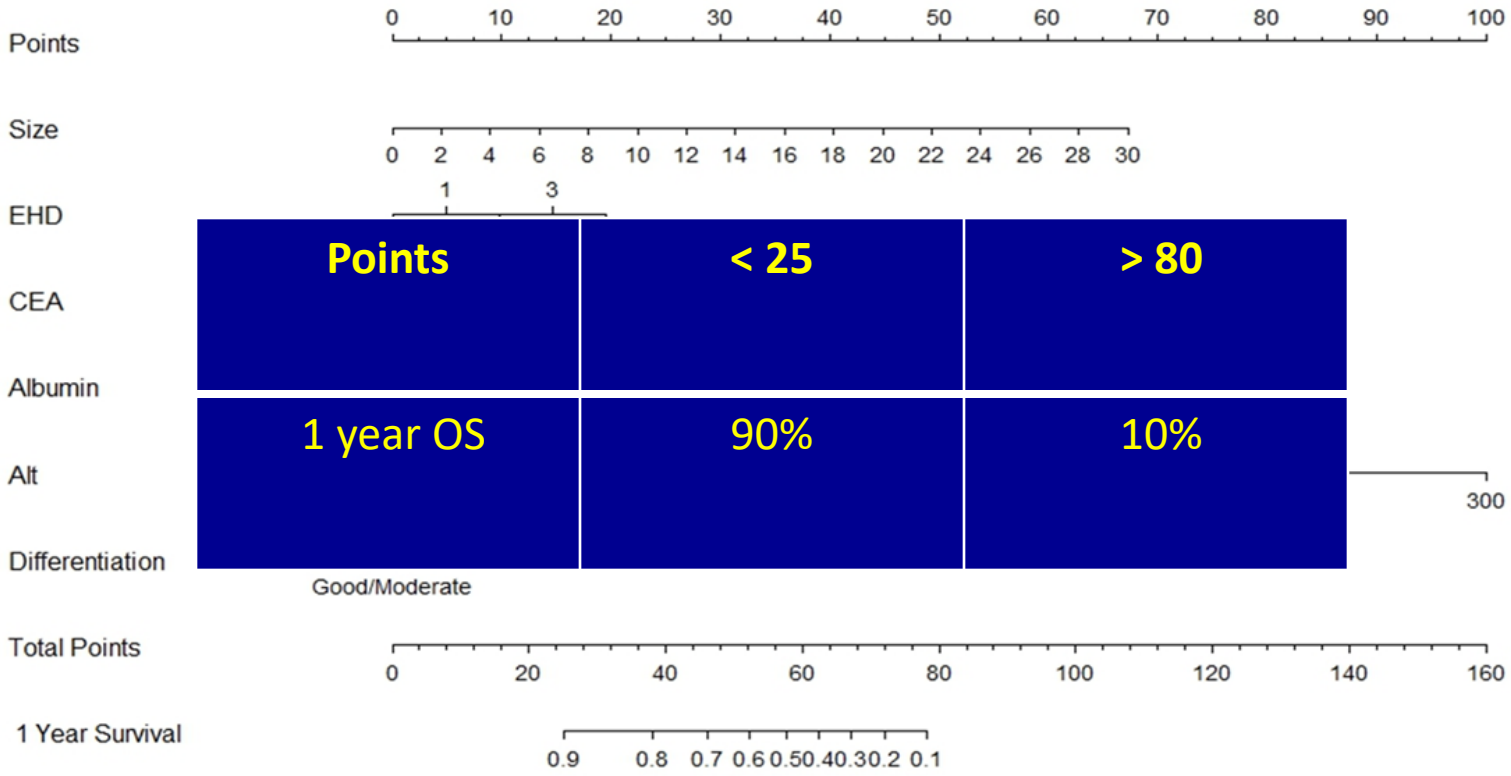


Gibbs et al: Clinical Colorectal Cancer December 2018

5 months prolongation of Median Survival and 36% protective effect against death

Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases

103 patients; 77% EHD, Median OS: 11.4 months



NOMOGRAM: 1-year OS of patients with total points of **<25 vs. >80 was 90% and 10%,** respectively

Bootstrap resampling showed **good discrimination** (optimism corrected c-index=0.745) and **calibration** (mean absolute prediction error=0.299) of the nomogram

Kurilova I, Gonen M, Cercek A, Kemeny NA, Sofocleous CT: Clinical Colorectal Cancer September 2019

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Does Locoregional Therapy make sense in Chemorefractory CLM?

- Median Survival: 5 (4-6) months
- TAS 102 and Regorafenib: survival benefit of 1.5 months over BSC
- IAT Justified with survival over 9 months
- Y90 Consistently results in median overall survival around 1 year at the chemorefractory stage (9-15 months)

- RCT of TAS 102 in refractory Metastatic CRC. Mayer RJ N Engl J Med 2015; 372 :1909-19
- Regorafenib monotherapy for previously treated CRC (CORRECT): RCT vs placebo Lancet 2013; 381:303-312

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PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIO

can be considered.

- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[15]

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Pulmonary Metastatectomy or Minimal Therapy?

Recurrence rates: 36%-58% after initial pulmonary resection.

Repeated thoracotomy improves survival but is associated with a higher morbidity because of the resection of more functional lung tissue and resulting deterioration of pulmonary function.

Therefore a Lung Preserving Treatment is very desirable

Shall we offer Ablation to Resectable patients too?

Mori M et al: Surgical resection of pulmonary metastases from colorectal adenocarcinoma. Special reference to repeated pulmonary resections. *Arch Surg 1991; 126:1297-301; discussion 1302*.

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Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases

T. de Baère[1*], A. Aupérin[2], F. Deschamps[1], P. Chevallier[3], Y. Gaubert[4], V. Boige[5], M. Fonck[6], B. Escudier[5] & J. Palussiére[7]

2002 -2010: Institut Gustave Roussy & Institut Bergonié)

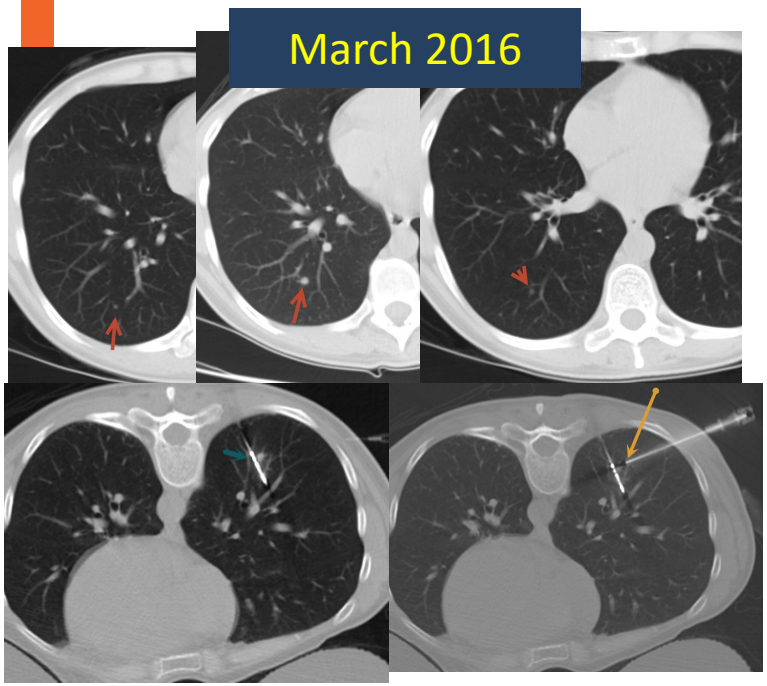
- **566 patients with 1037 metastases: 4-70 mm**
- 1, 3-and 5-years OS rates: 92.4%, 67.7%, 51.5%
- **188 patients with 293 colorectal cancer metastases**

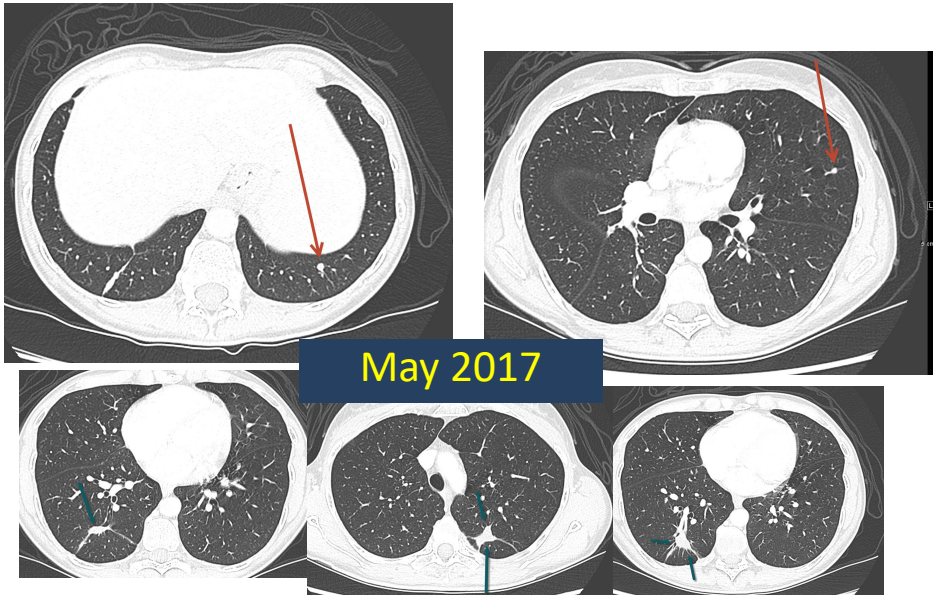
- Factors affecting PFS ad OS

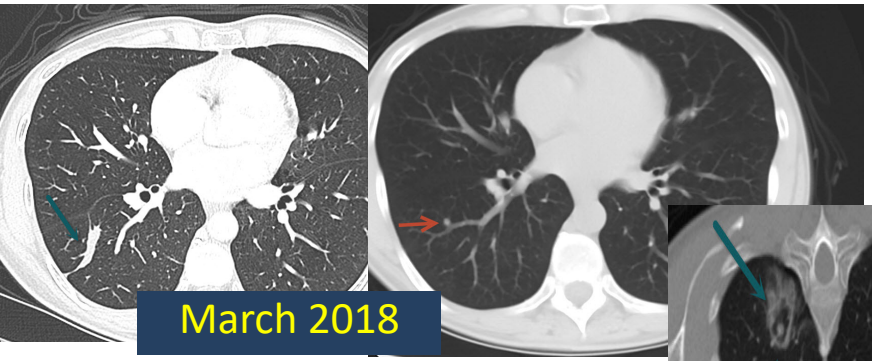
  - Primary other than colon or kidney
  - size >2cm (HR=2.10, *p*=0.0027) and
  - number of metastases ≥3 (HR=1.86, p=0.011)

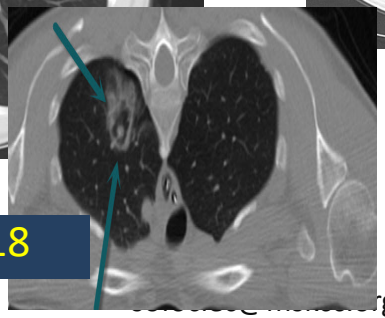
T. de Baère, Palussiére et al Radiofrequency ablation is a valid treatment option for lung metastases: Experience in 566 patients with 1037 metastases Annals of Oncology Advance Access published February 16, 2015

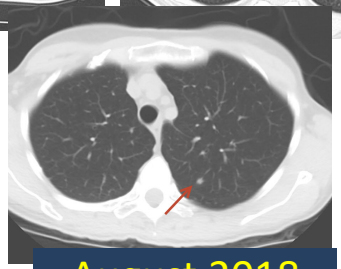
40 yo Female with Rectal Cancer: From March 2016-September 2018: Eight Ablations in 5 sessions









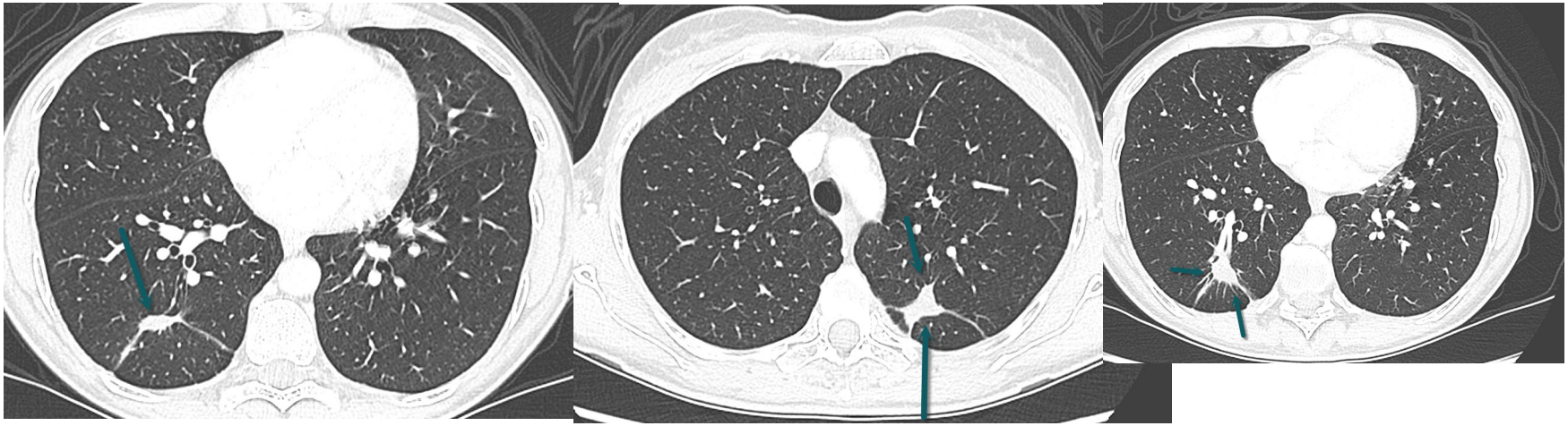


2016-2019

March 2016-September 2018: 9 Ablations in 6 sessions:
40 yo Female with Rectal Cancer

Over 3 Years disease Control without Chemotherapy

Over 50% of patients got a Chemo Holiday for more than 20 months through repeat Ablation



Petre, NE et al: Treatment of Pulmonary Colorectal Metastases by RFA Clinical Colorectal Cancer, Vol. 12, No. 1, 37-44
Kurilova I, et al: MWA in CRC Pulmonary Metastases: CVIR 2018 Oct 9410 10: 1530-44

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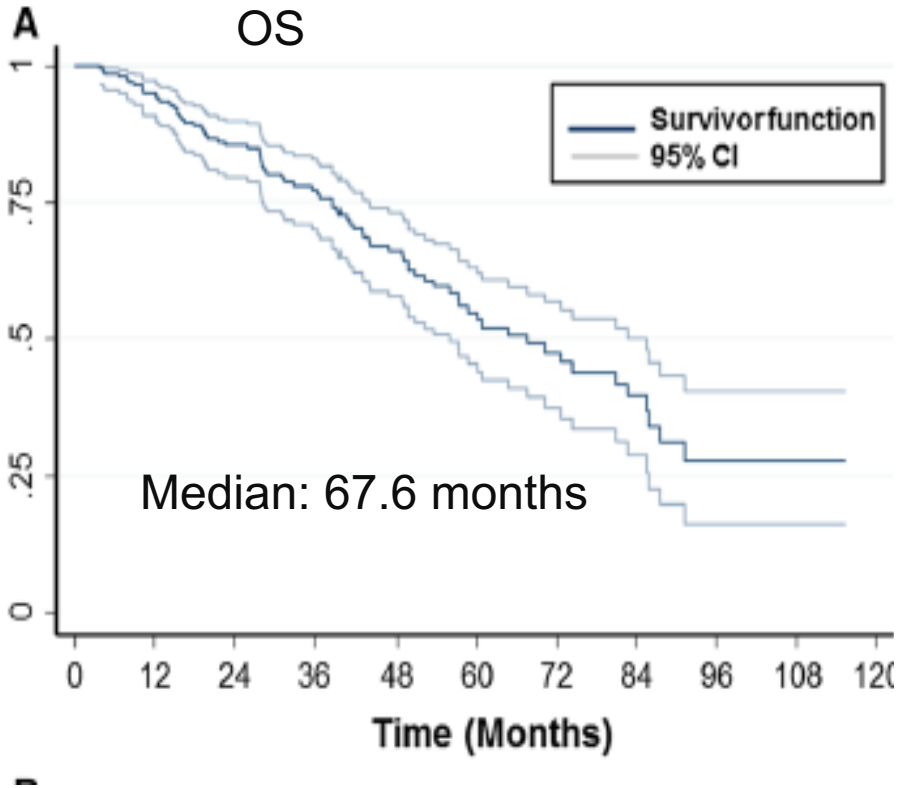
CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Pulmonary Thermal Ablation Enables Long Chemotherapy-Free Survival in Metastatic Colorectal Cancer Patients

Mariane Fonck[1] · Jean-Thomas Perez[2] · Vittorio Catena[2] · Yves Becouarn[1] · Laurent Cany[3] · Eric Brudieux[4] · Laure Vayre[5] · Patrick Texereau[6] · Valérie Le Brun-Ly[7] · Véronique Verger[8] · Véronique Brouste[9] · Dominique Bechade[1] · Xavier Buy[2] · Jean Palussière[2]

209 patients 323 ablation sessions for 630 CRC lung metastases

Chemotherapy Free Survival CFS : time interval between ablation and resuming CT or death without resuming the CT



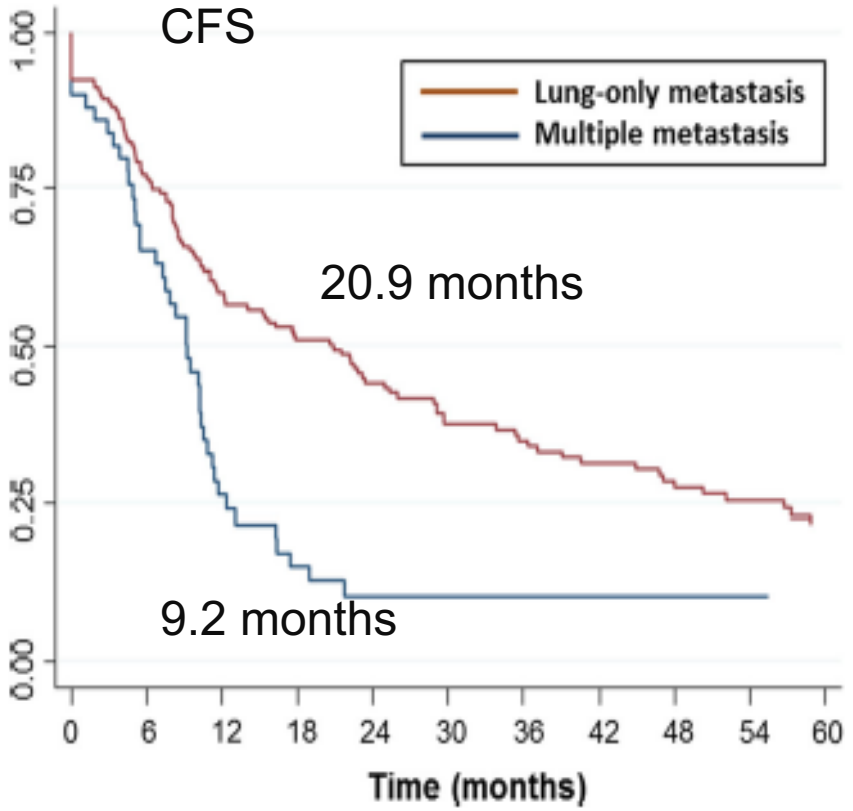
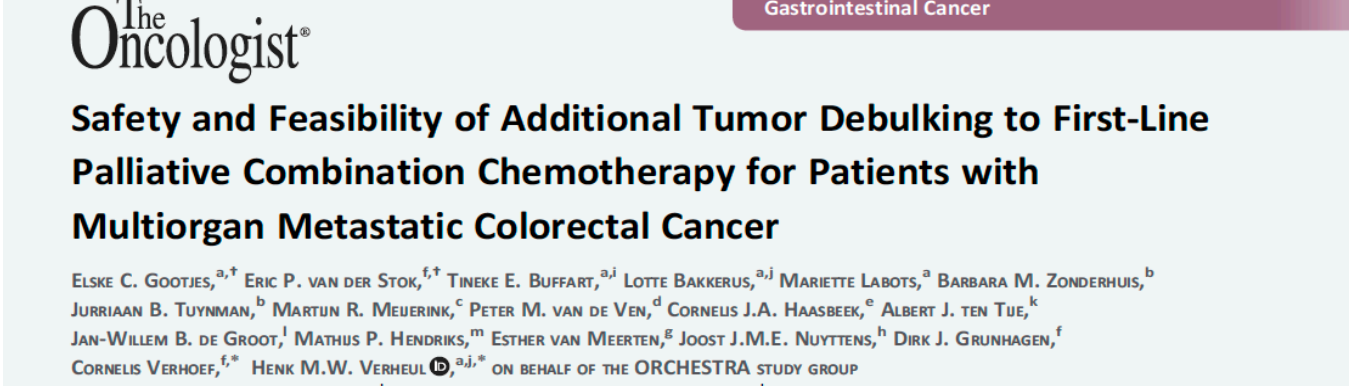


Fig. 2 Chemotherapy-free survival lung-only metastases (red curve) multiple metastases (blue curve)



Eligible if 80% debulking feasible: RX, TA, RT after 3-4 cycles: 5FU/LV, CAP+OX+/-Bev

Randomization: Debulking with SOC vs. SOC Alone

88 patients: Debulking 45 vs. SOC 43

Debulking in 37/45: 2 no lesions, 5 POD, 1 died.

15/37 (40%) adverses events and post op Mortality 2.7%

Post-Debulking chemo 89%

Trials in Progress:
Value of Debulking EHD CRC OMD

ORCHESTRA: 80% debulking with SOC (NCT01792934)
Aims to prove safety and feasibility in 100 patients

MCT phase III synchronous unresectable CRC mets
SOCch vs Resection of Primary followed by SOCch:
Netherlands, France: NCT02363049, NCT02314182 Germany: ISRCTN30964555
China: NCT02149784

LUNA Trial: Phase II single institution Randomized
Resectable Liver mets and unresectable (but low volume) lung mets between RX+SOCch vs SOCch only

Conclusions: IO in Oligometastatic CRC

OMD and tumor burden are significant factors affecting outcomes

Low volume disease that can be treated locally can improve PFS and OS

The exact role and timing of locoregional Therapy need be optimized via prospective studies

An emerging role of locoregional therapy in CRC oligometastatic disease is disease control while allowing for long chemotherapy free intervals.

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