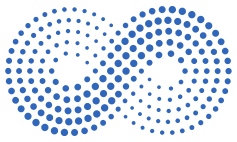
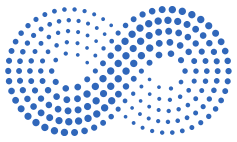


Local Management of Lung Metastases: Anything New?

Marcelo Cypel MD, MSc, FACS, FRCSC
Surgical Director, UHN Transplant and ECLS Program
Canada Research Chair in Lung Transplantation
Co-Director Pulmonary Metastases Program at UHN
Professor of Surgery, Division of Thoracic Surgery
University of Toronto, University Health Network



- No disclosures related to this presentation

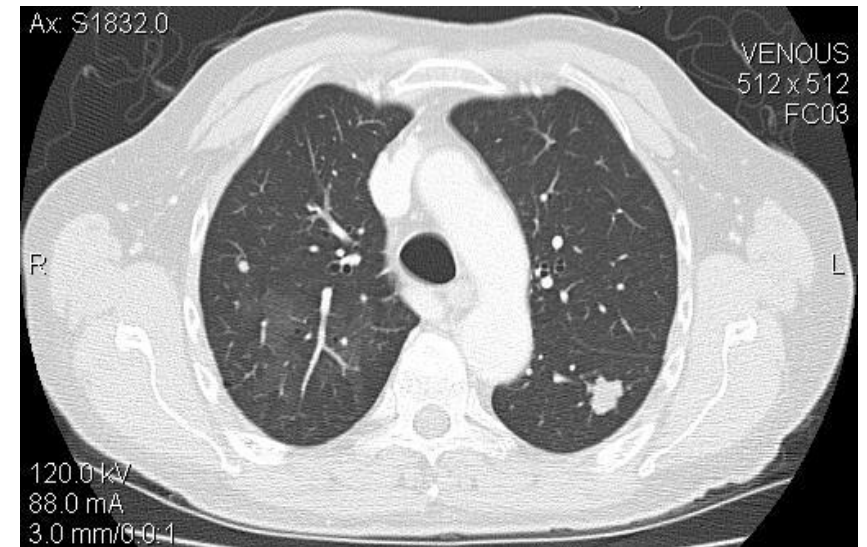


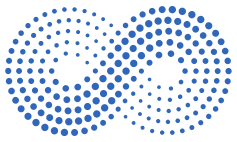
Pulmonary Metastases: Questions?

1) Are local therapies going to be helpful?

2) If so, what modalities to use?

- Surgery
- SBRT
- Conventional Radiation
- RFA





Pulmonary Metastases: Questions?

1) Are local therapies going to be helpful?

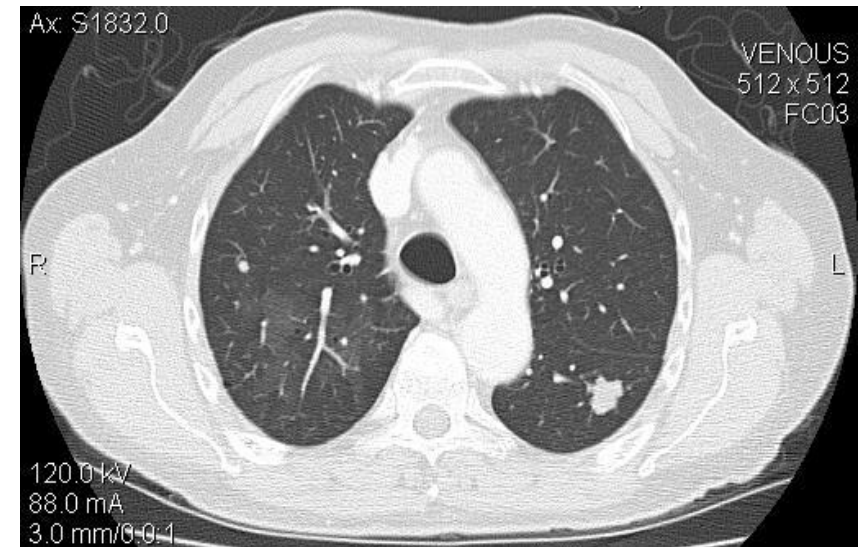
2) If so, what modalities to use?

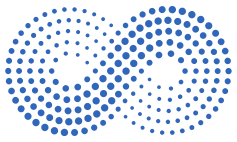
- Surgery

- SBRT

- Conventional Radiation

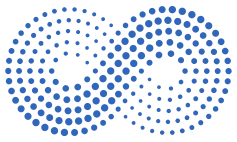
- RFA





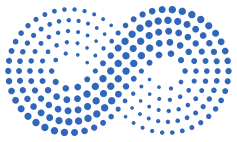
Is a Local Therapy Indicated?

- Age and comorbidities
- Pathology of primary tumour (colon ca/sarcoma vs. melanoma/breast ca)
- Timeline of disease course (DFI, rate of growth)
- Number and Location of lung metastases
- Extra-pulmonary disease (lymphnodes, other organs)

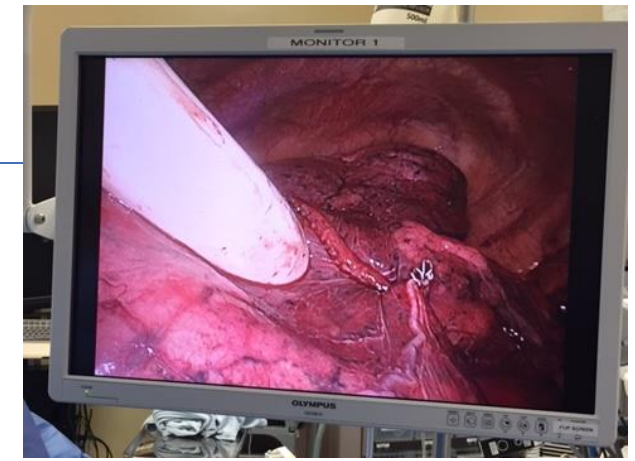


In selected patients: YES

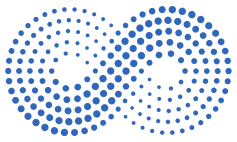
What modality?



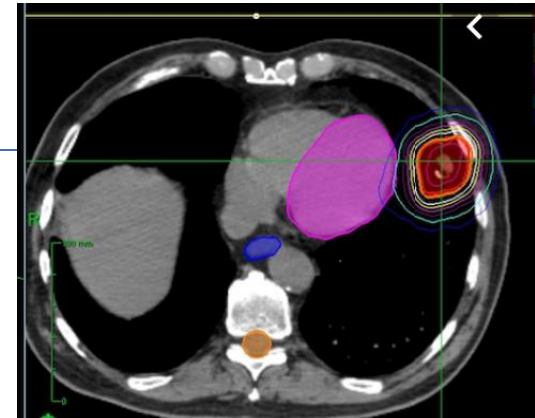
Surgery (Pros)



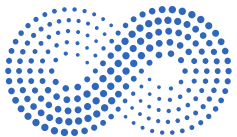
- Well established approach for PM
- Minimal invasive approaches leading to faster recovery and easy reinterventions
- Local recurrence (at the resection site) not common when appropriate margins are obtained
- Can provide long term survival
- Provide tissue diagnosis (important confirmation, or mutation testing in Oligoprogression)



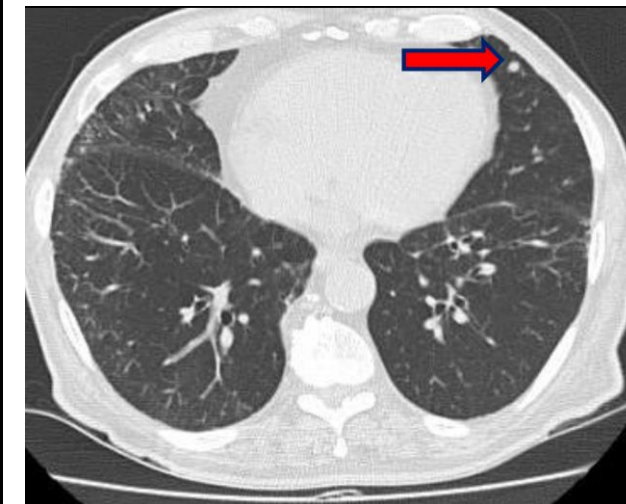
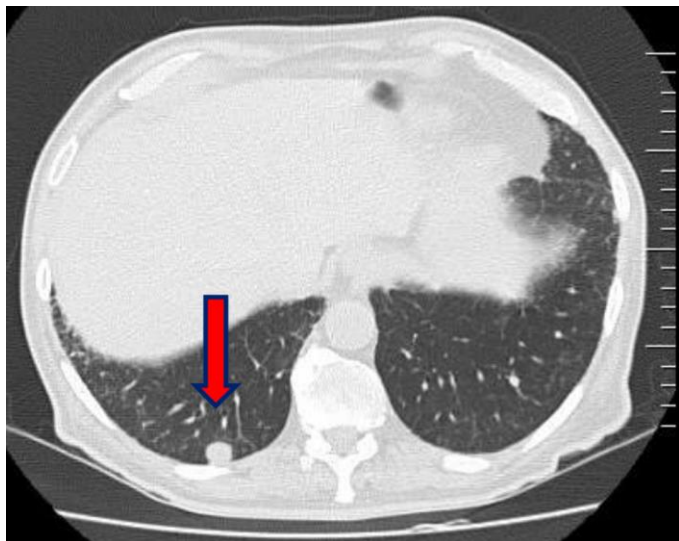
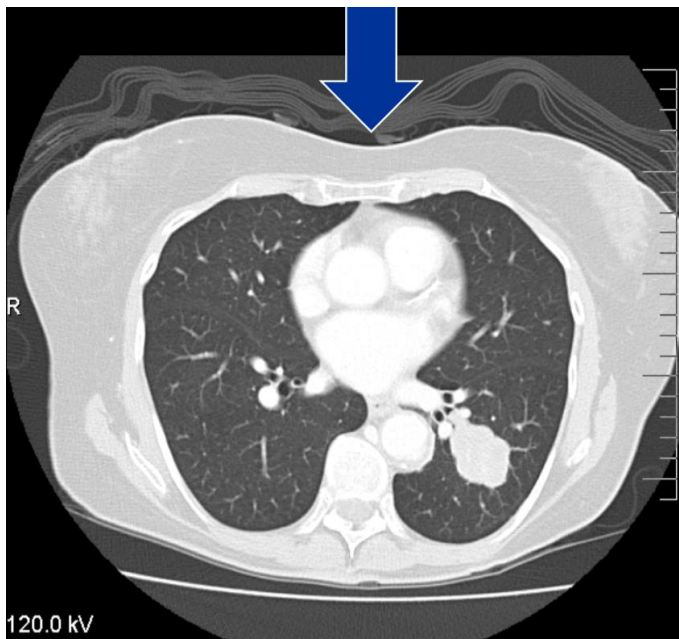
SBRT (Pros)

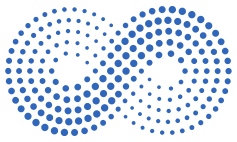


- Very well tolerated— Patients can work while on treatment
- Minimal side effects: Fatigue last few days.
- 3-5 days of treatment (1h each)
- Does not preclude other treatments immediately after (surgery or chemotherapy)



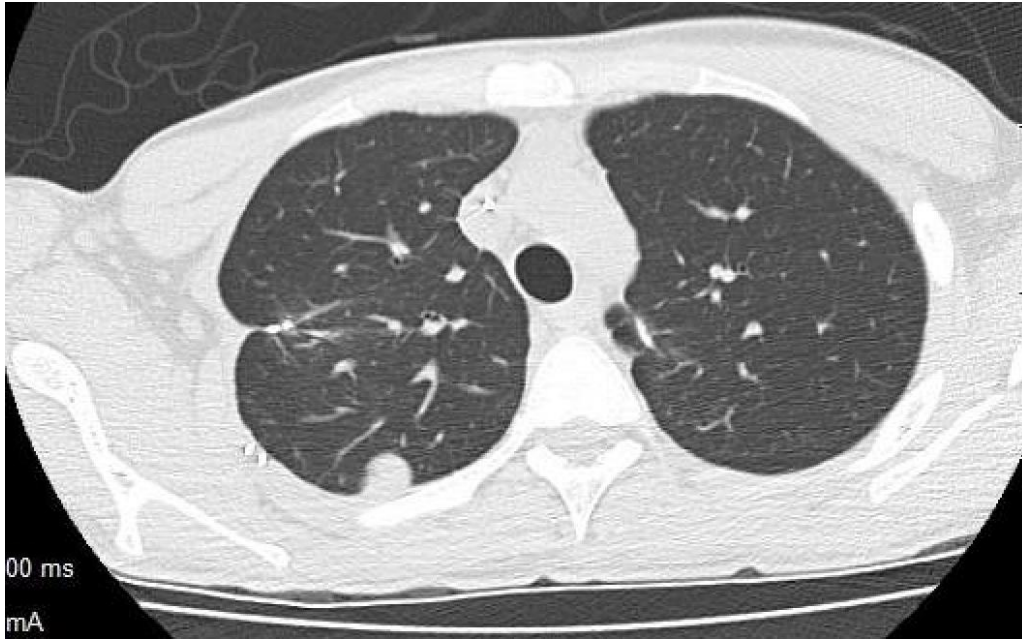
Challenges for SBRT





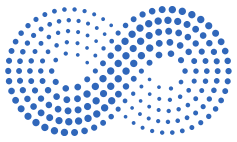
SBRT failures...

Oct 2017



March 2018





SBRT failures...

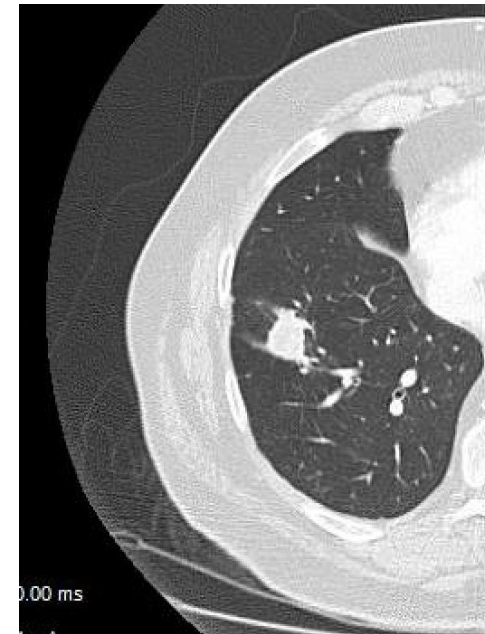
2016

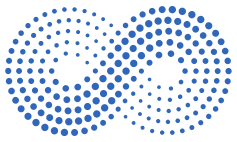


2017

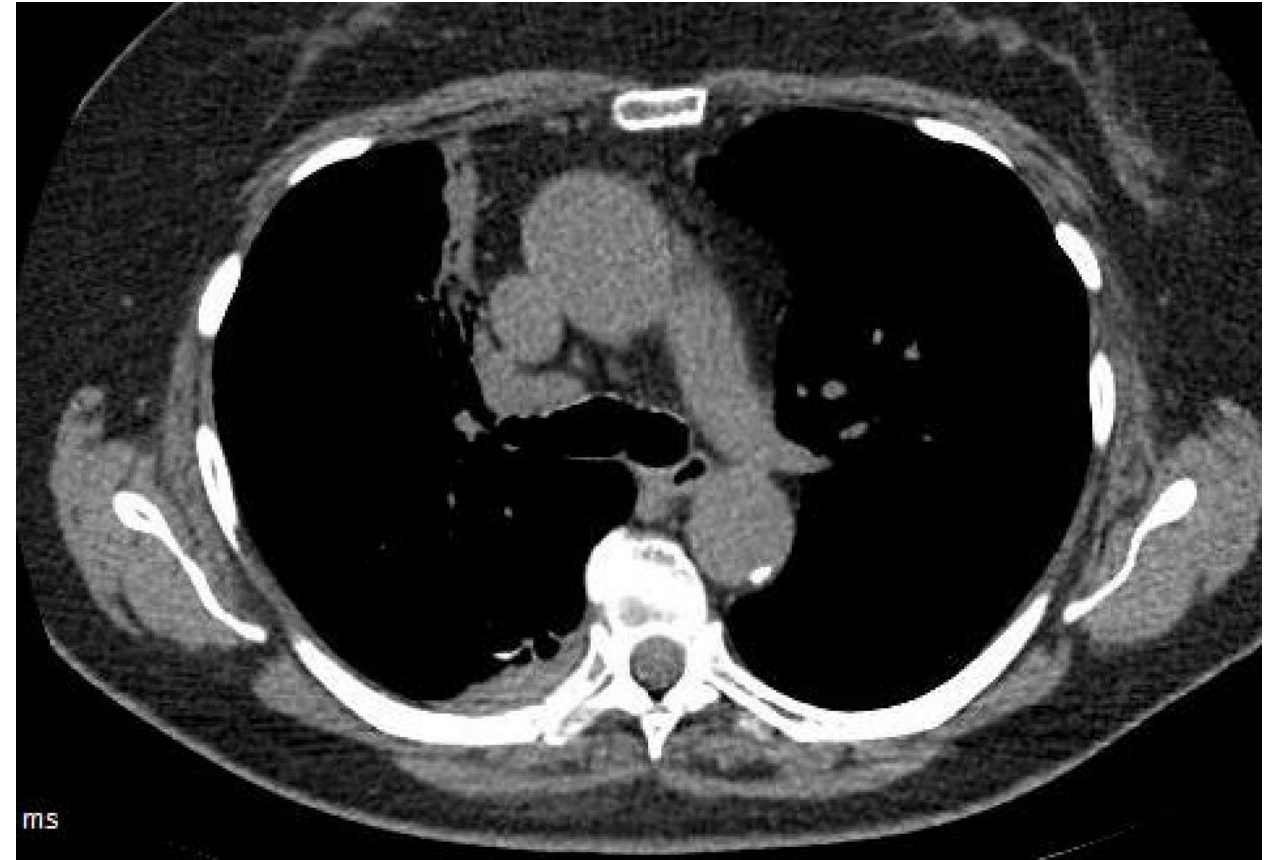
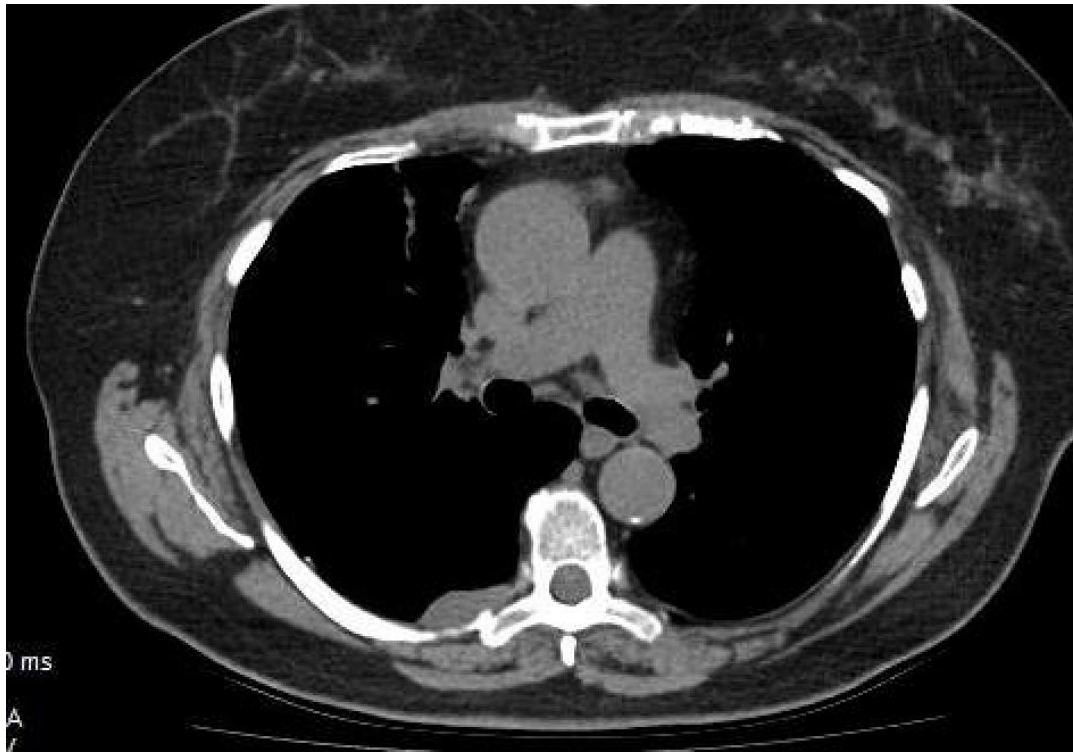


2018





Rib fracture and chronic pain after SBRT



Local failure after stereotactic body radiation therapy or wedge resection for colorectal pulmonary metastases

David B. Nelson, MD, MSc,^a Nabihah Tayob, PhD,^b Quynh-Nhu Nguyen, MD,^c Jeremy Erasmus, MD,^d Kyle G. Mitchell, MD,^a Wayne L. Hofstetter, MD,^a Boris Sepesi, MD,^a Mara B. Antonoff, MD,^a and Reza J. Mehran, MD^a

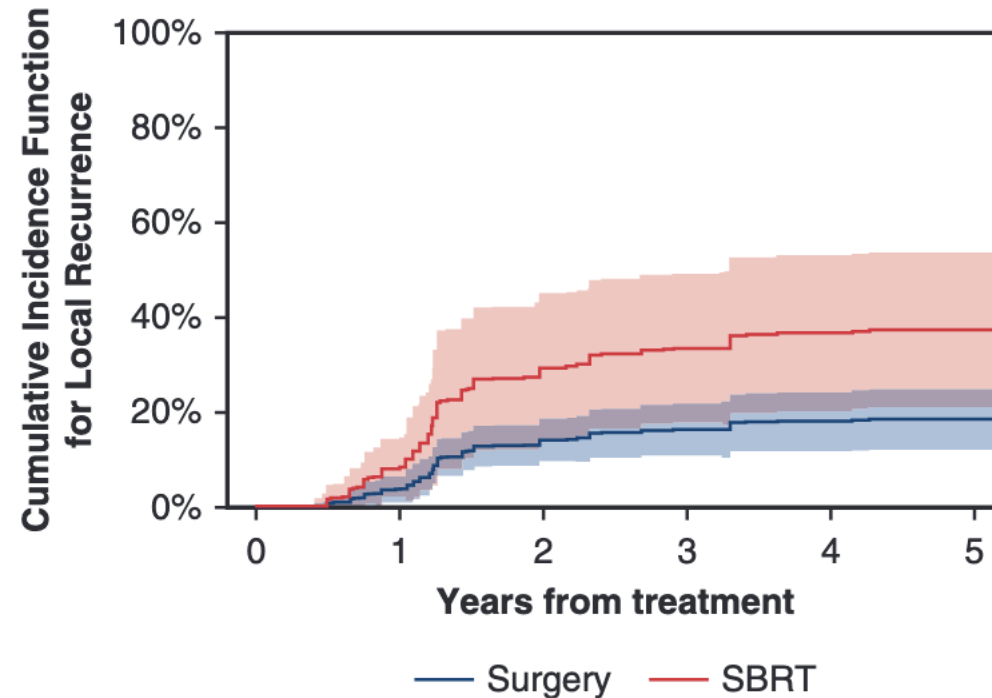
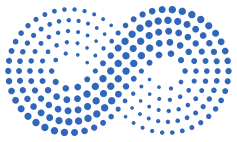


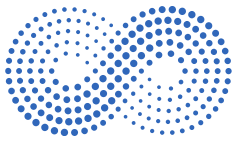
FIGURE 2. Cumulative incidence function indicating risk of local recurrence is higher with SBRT compared with wedge resection. Results modeled with death as a competing risk using matching weights. *SBRT*, Stereotactic body radiation therapy.

When we Consider SBRT in Lung Mets?

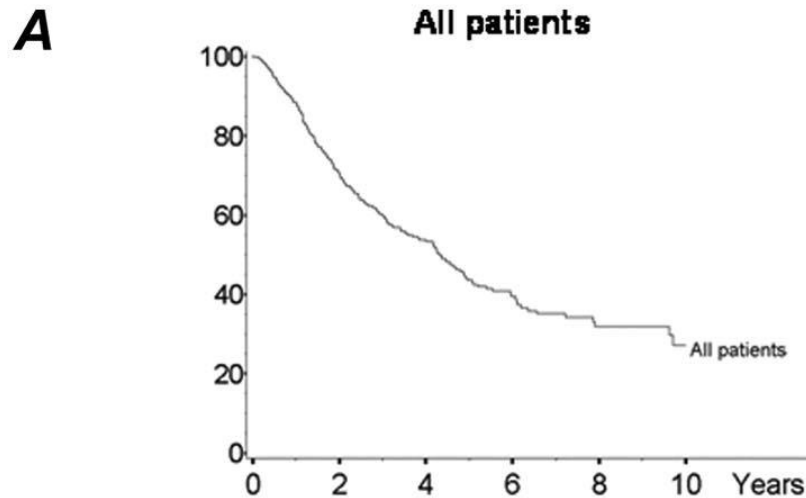
- Lesion requiring a lobectomy in a patient with high chance of future recurrence in other parts of the lungs
 - Multiple lung lesions where a VATS would be possible if some lesions are treated with SBRT
 - Patient with multiple medical comorbidities requiring bilateral surgery - consider SBRT in one side
 - Not surgical candidate
-



General Principles

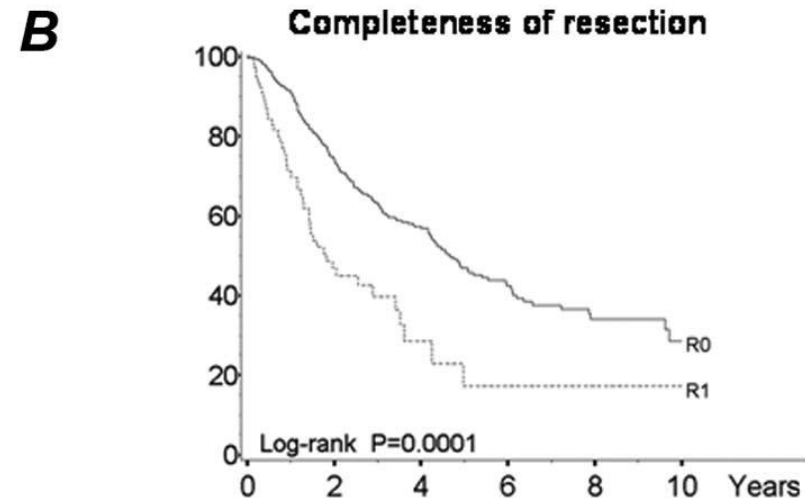


A 10-Year Single-Center Experience on 708 Lung Metastasectomies: The Evidence of the “International Registry of Lung Metastases”



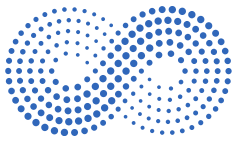
N° at risk	
All patients	575 296 142 57 27 10

All patients	Overall Survival (%)			
	<u>1-year</u>	<u>2-year</u>	<u>5-year</u>	<u>10-year</u>
	89	71	43	27

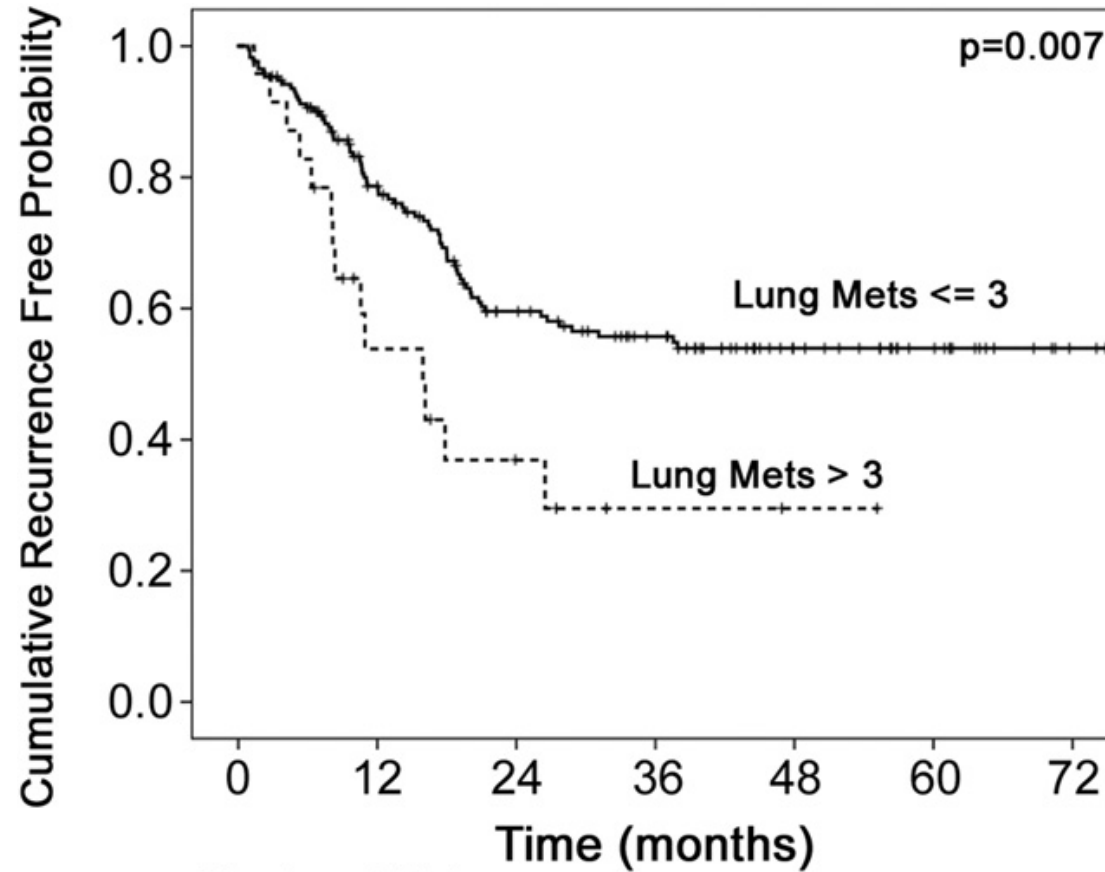


N° at risk	
R0	490 271 135 56 26 9
R1	85 25 7 1 1 1

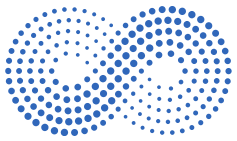
R0	R1	Overall Survival (%)			
		<u>1-year</u>	<u>2-year</u>	<u>5-year</u>	<u>10-year</u>
		91	74	46	29
		72	47	20	20



Lung recurrence after pulmonary metastasectomy for CRC

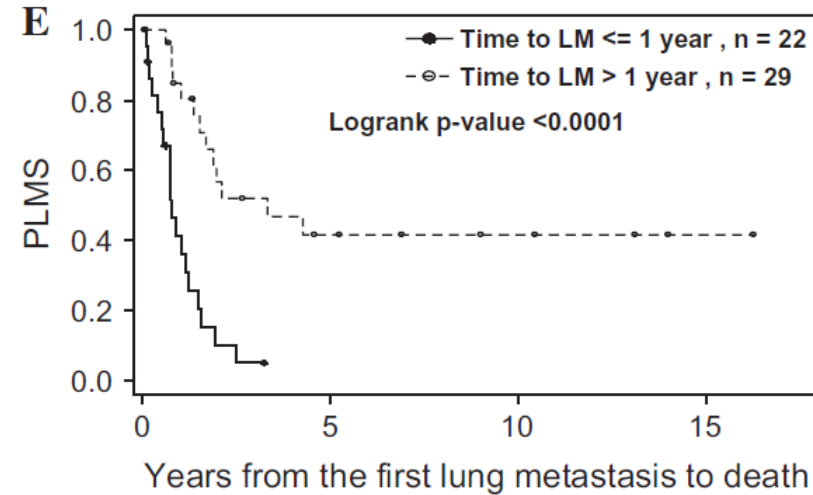
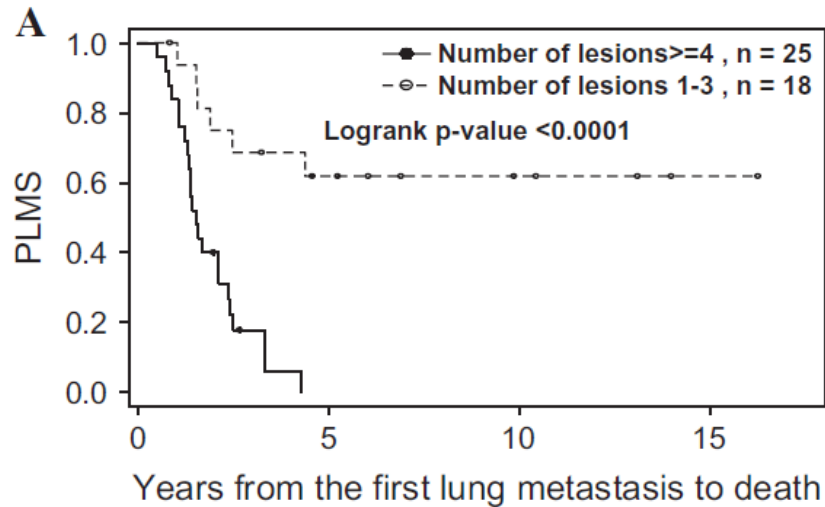


Blackmon SH, Ann Thorac Surg. 2012 Dec;94(6):1802-9



Toronto data

More than 3 lesions or < 1 year DFI = no survivors at 5 years (osteosarcoma)



Annals of Oncology 20:1136-1141, 2009

RESEARCH

Open Access

Prognostic factors in pulmonary metastasectomy and efficacy of repeat pulmonary metastasectomy from colorectal cancer



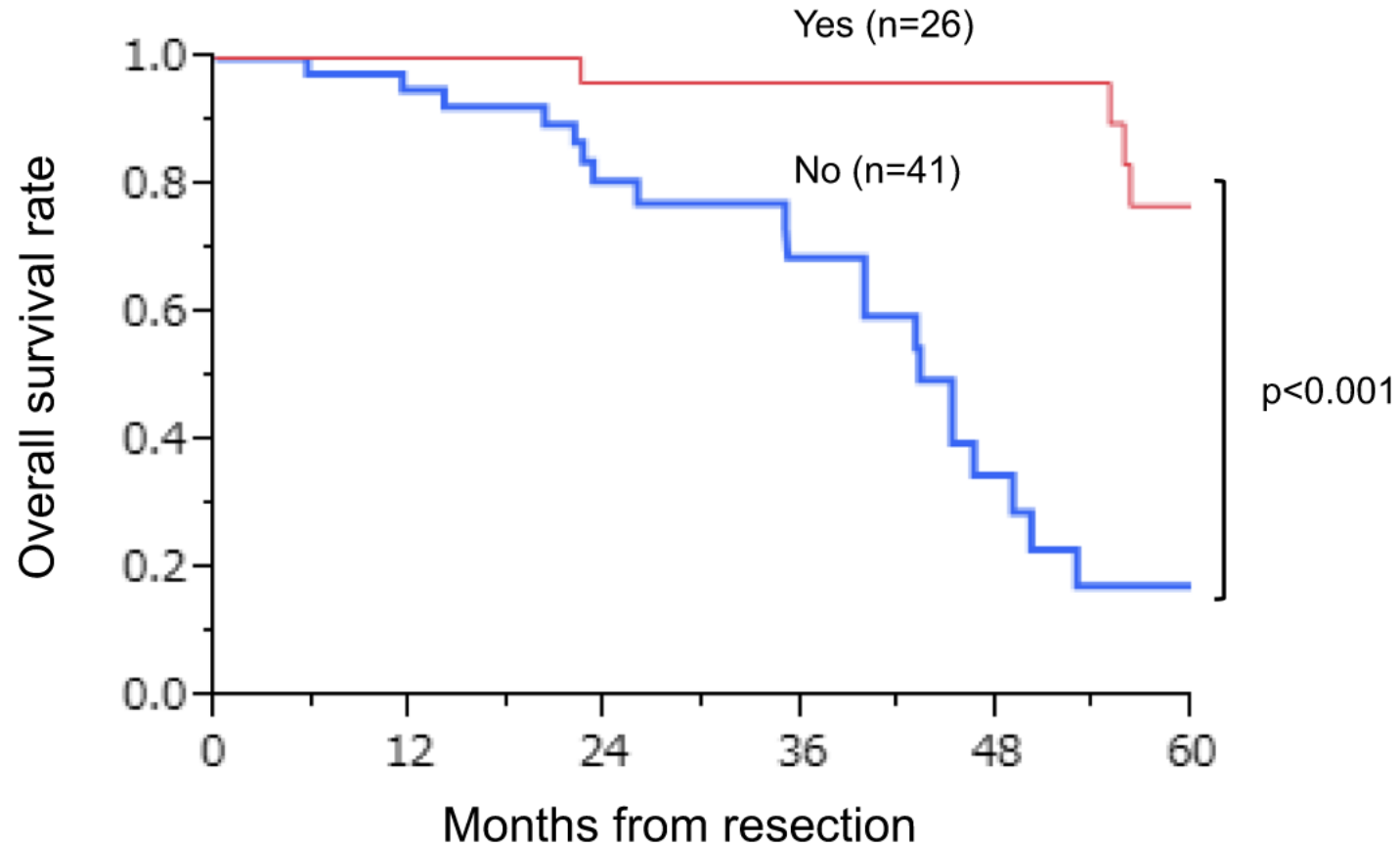
Table 5 Survival of the pulmonary metastasectomy from CRC in multivariate analysis

Prognostic factors	<i>p</i> value	Risk ratio	95% confidence interval
Gender (male/female)	0.60	1.324	0.484–4.381
Past history of extra thoracic metastasis (presence/absence)	0.67	1.205	0.511–2.922
Preoperative CEA level (elevated/normal)	0.89	1.083	0.356–3.547
Maximum tumor size (≥ 20 mm/ < 20 mm)	0.74	1.203	0.401–3.646
Mediastinal lymph node metastasis (positive/negative)	0.02*	8.206	1.566–34.962
Repeat pulmonary metastasectomy for the pulmonary recurrence (yes/no)	< 0.001 ***	0.054	0.010–0.202

CRC colorectal cancer, CEA carcinoembryonic antigen level, normal upper limit at 5 ng/ml

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Repeat pulmonary metastasectomy for pulmonary recurrence



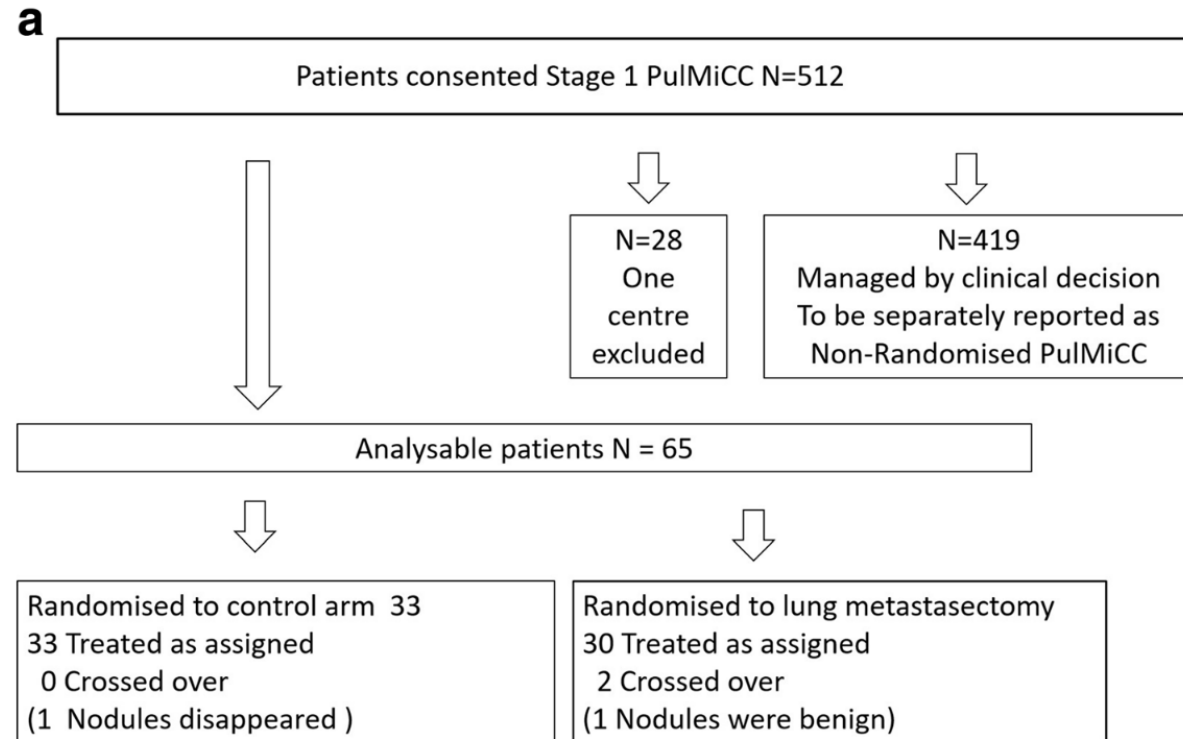
Patient at risk

Yes	26	26	25	19	17	10
No	41	38	25	16	7	2

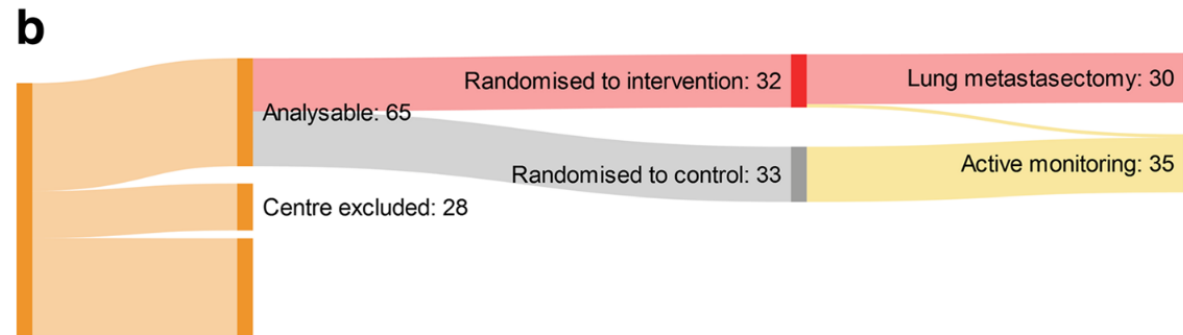
Fig. 4 Repeat pulmonary metastasectomy for the pulmonary recurrence and survival.

(PulMiCC Trial)

Pulmicc

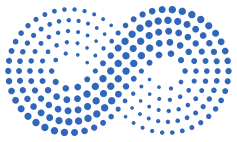


38% 5 year survival vs. 29% controls

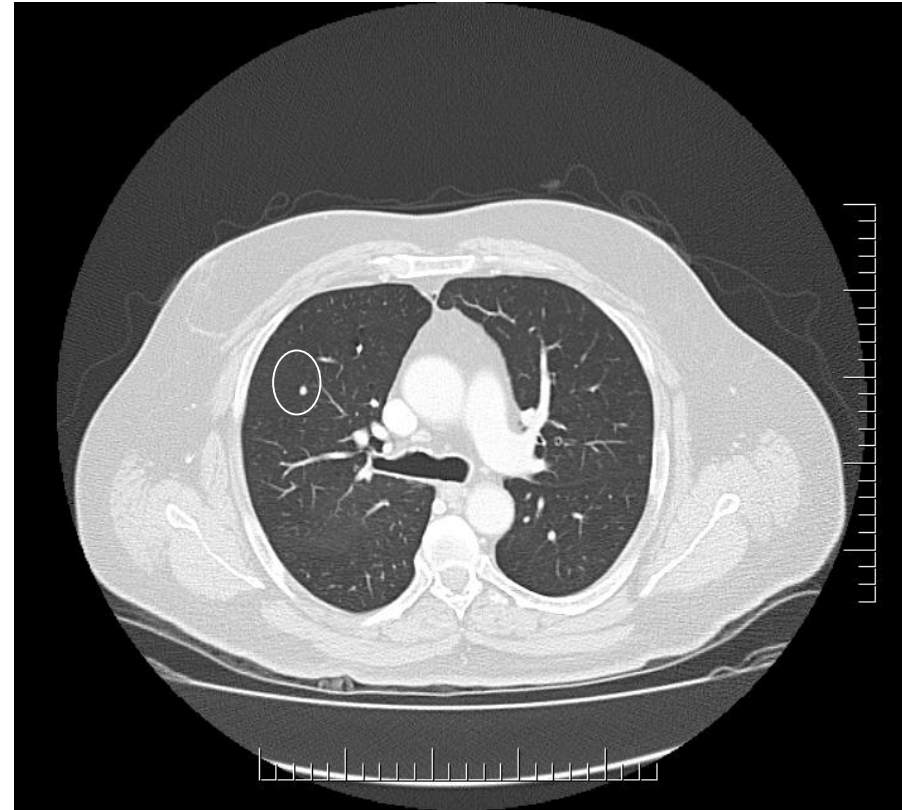
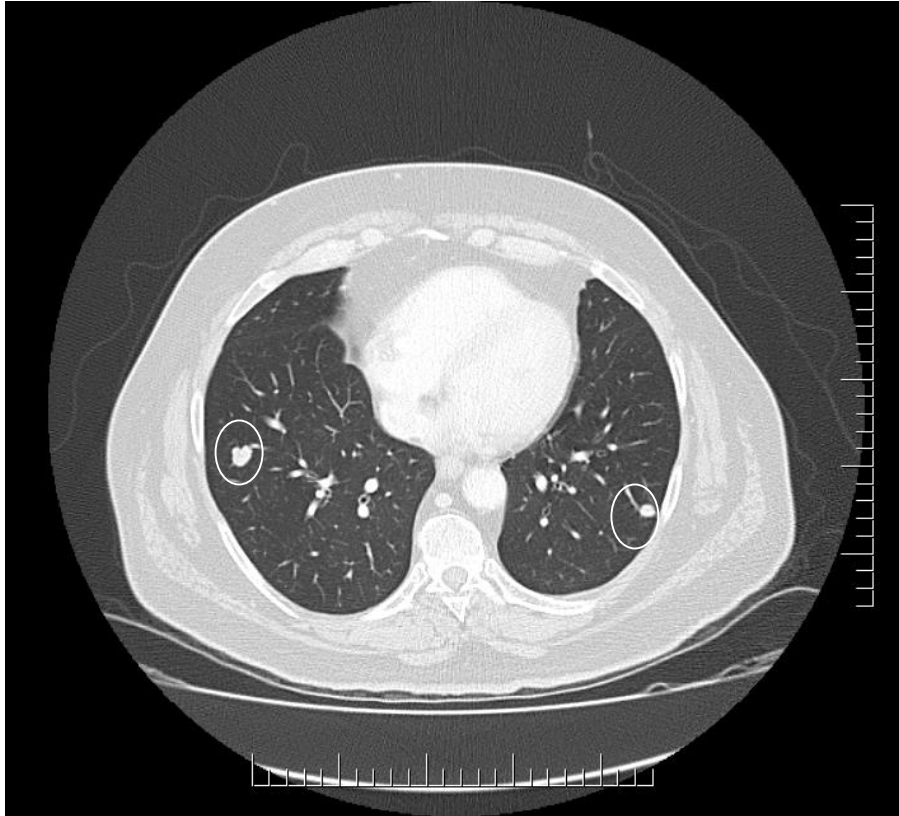


Lung Metastases Clinic: Princess Margaret Cancer Center

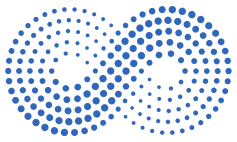
- 100% new consults (6-8/week) are discussed multi-disciplinary group: 2 surgeons, 1 rad onc, referring physician, med onc, thoracic radiologist
- Very often more lesions are found on imaging review than reported
- Plan is made in multidisciplinary fashion



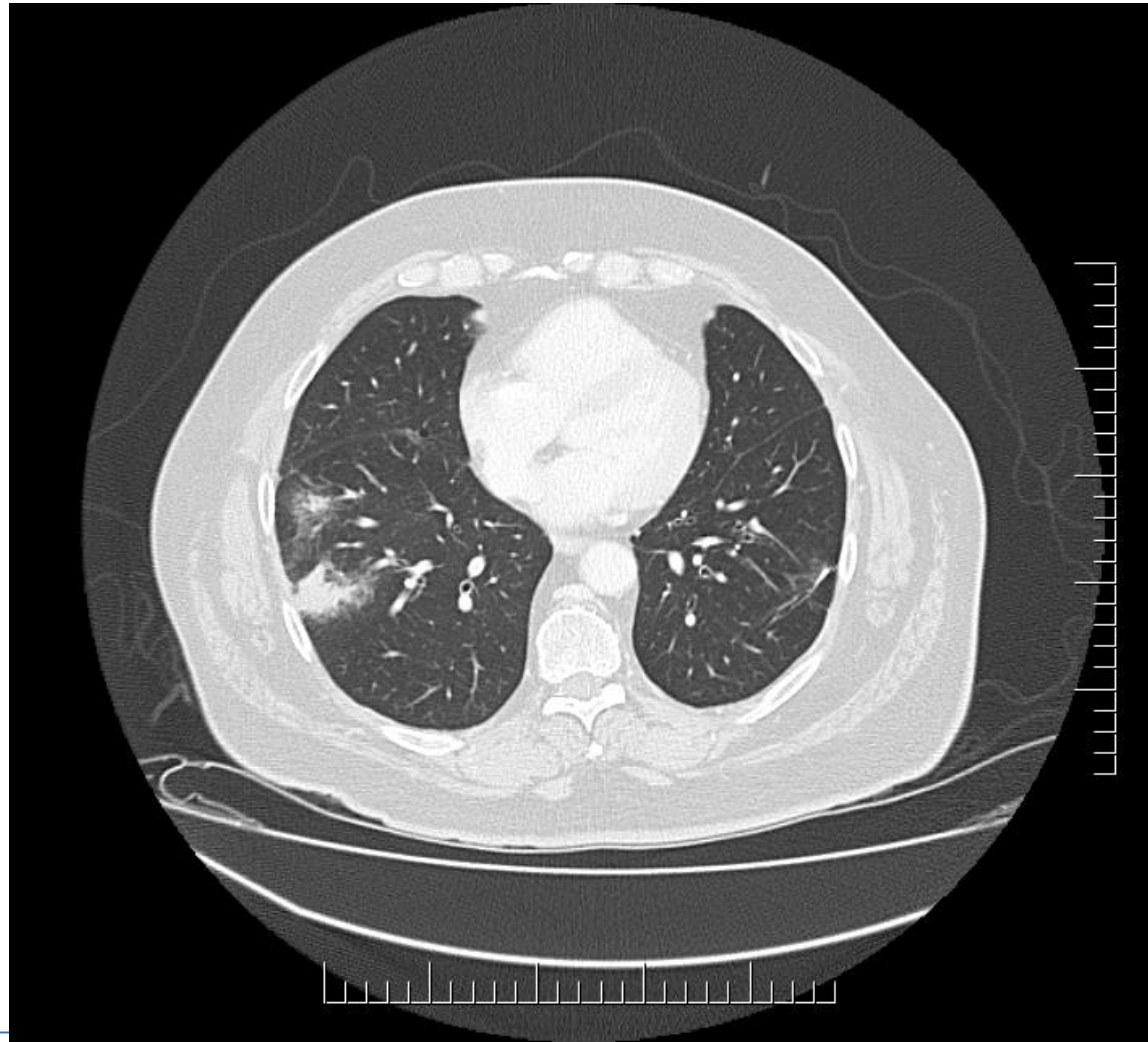
76 y old colorectal cancer resected 2y prior

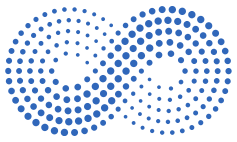


SBRT right sided lesions. VATS wedge LLL

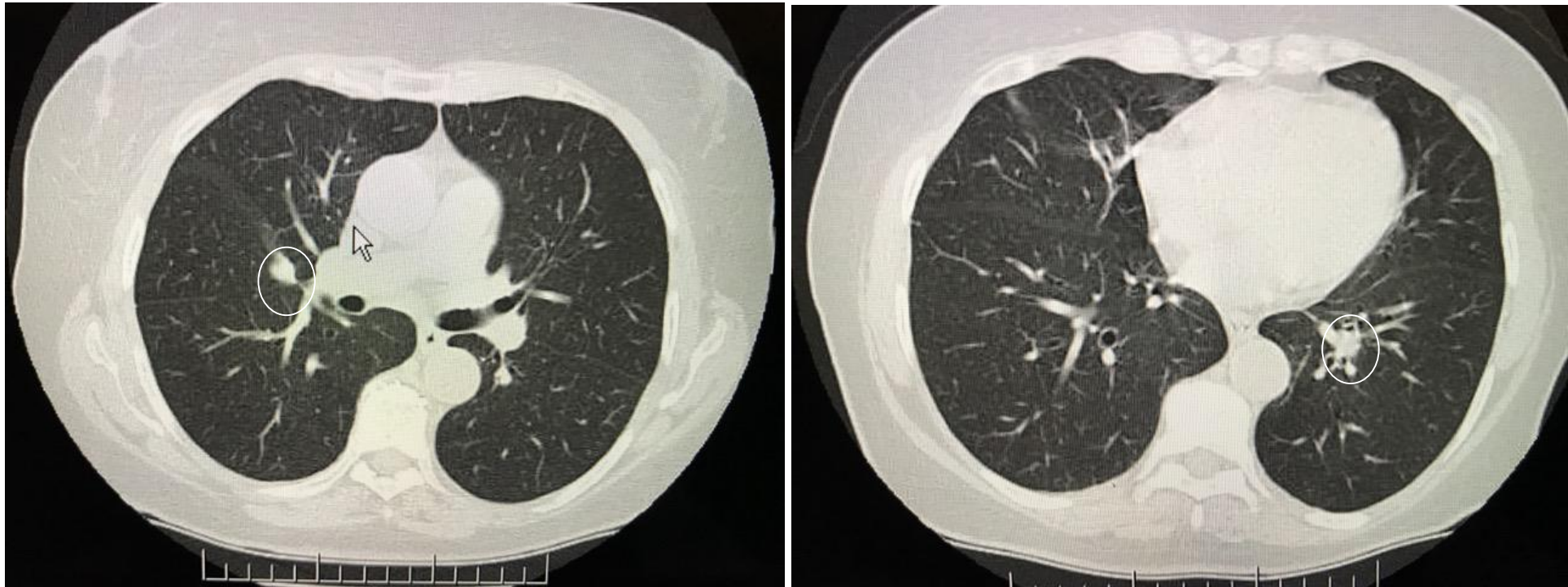


6 months- post treatment





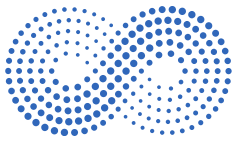
75y female.



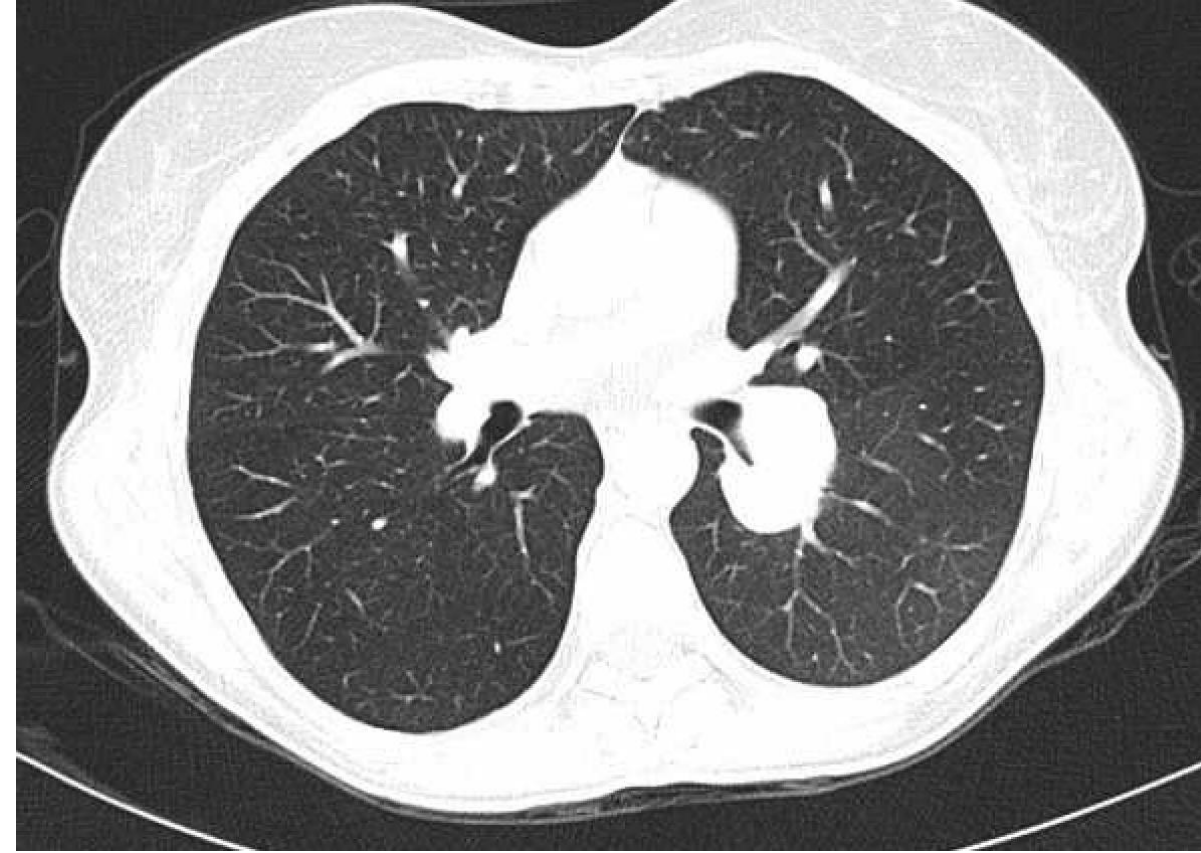
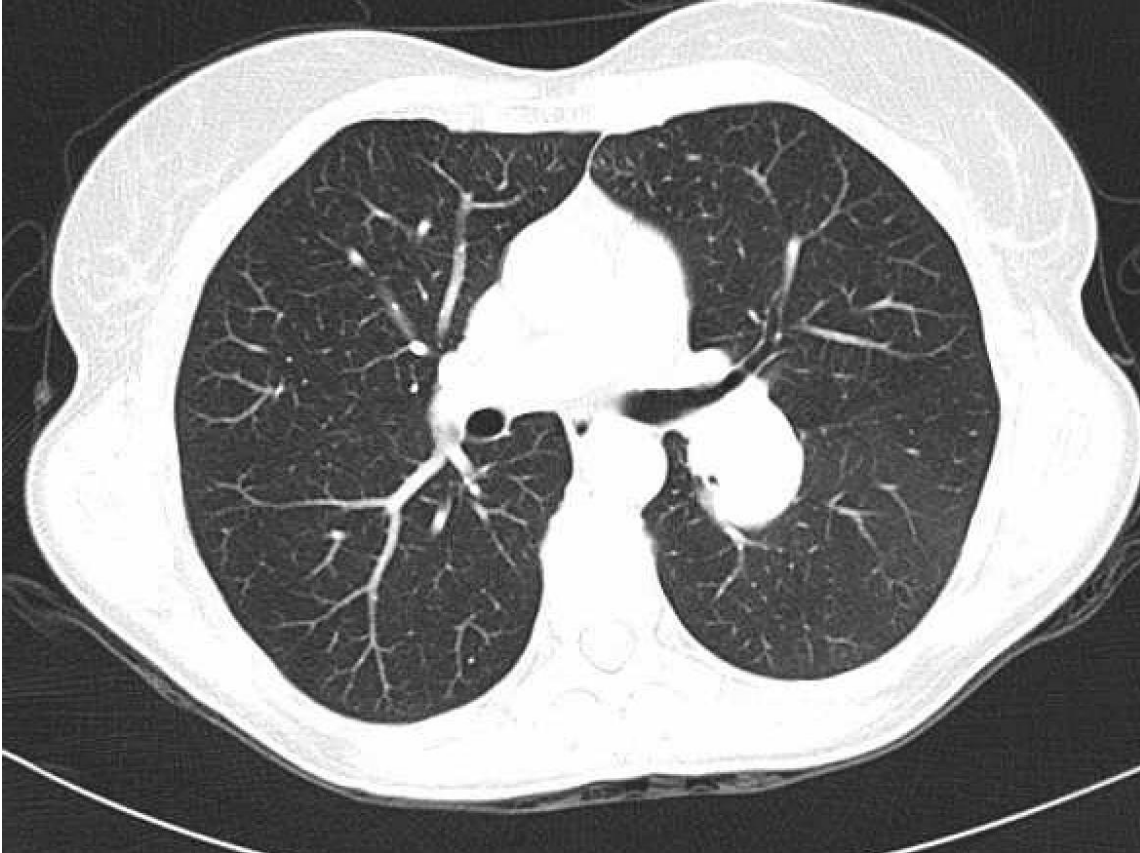
SBRT Right hilar lesion and VATS segmental resection LLL

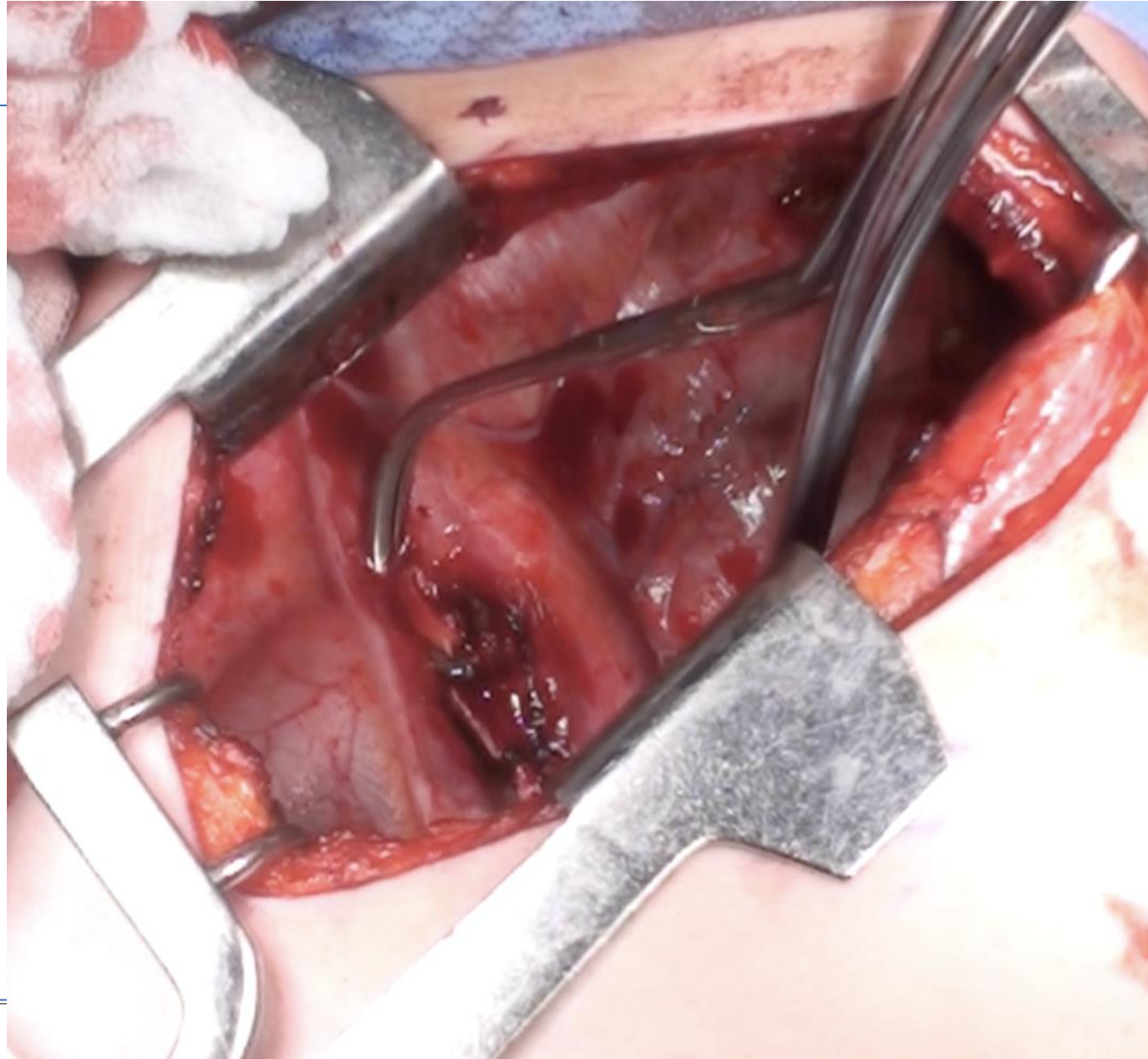
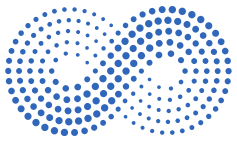
Conclusions I

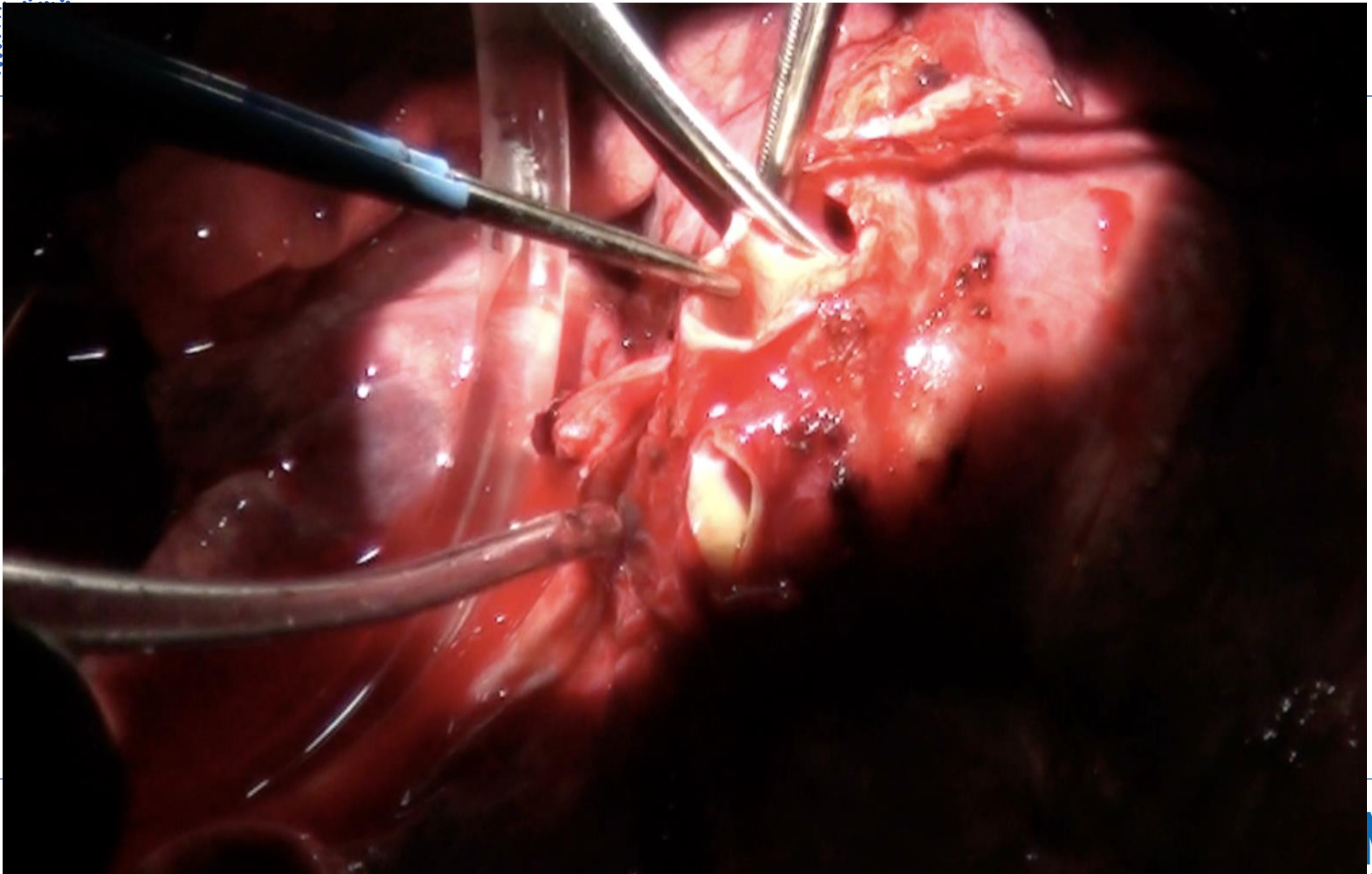
- Both surgery and SBRT results in good local control and low toxicity in well selected patients with lung metastases and they should be seen as complementary options
- Only a randomized CT can answer one is superior
- Patient selection is the most important
- Multidisciplinary input and detailed planning is essential (i.e. Lung Metastasis Clinic at UHN)

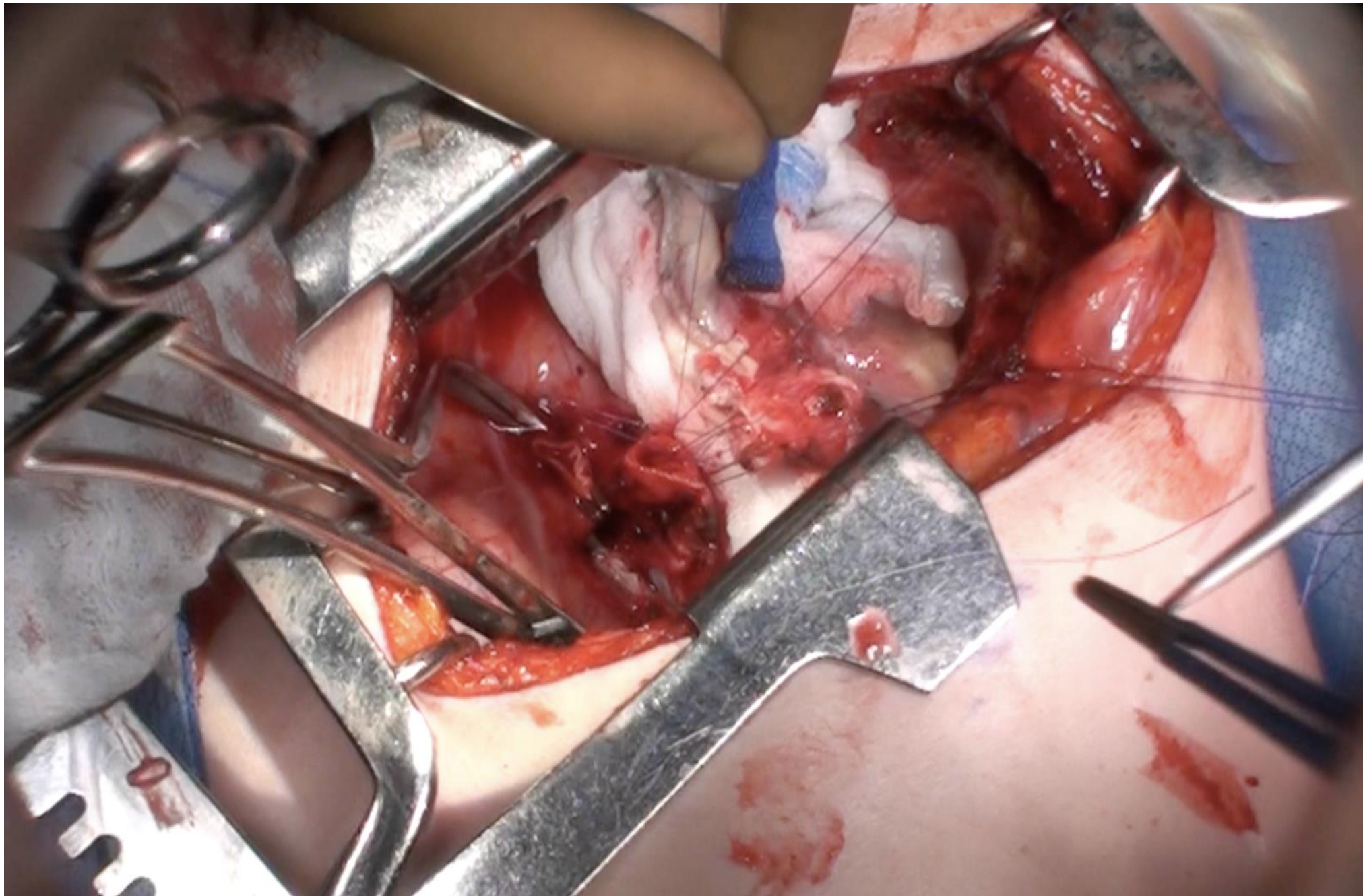


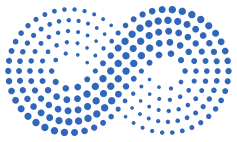
Complex Surgery

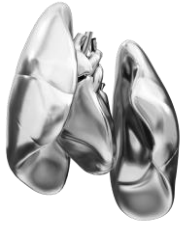






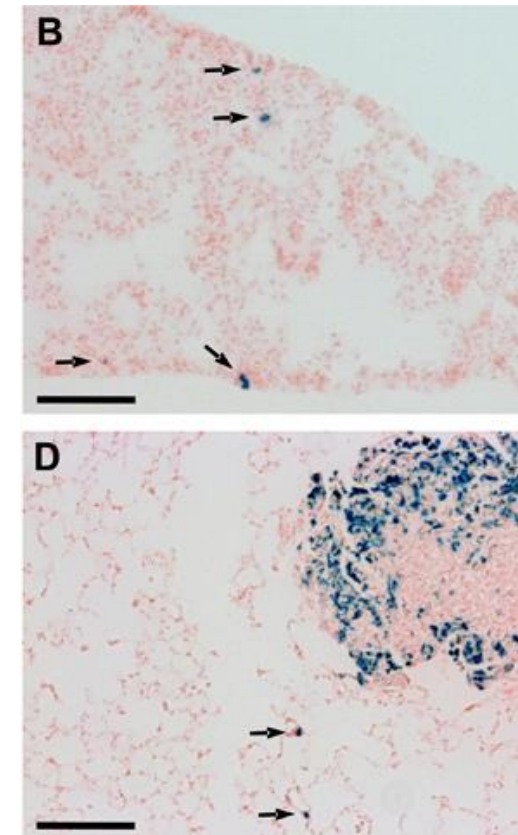
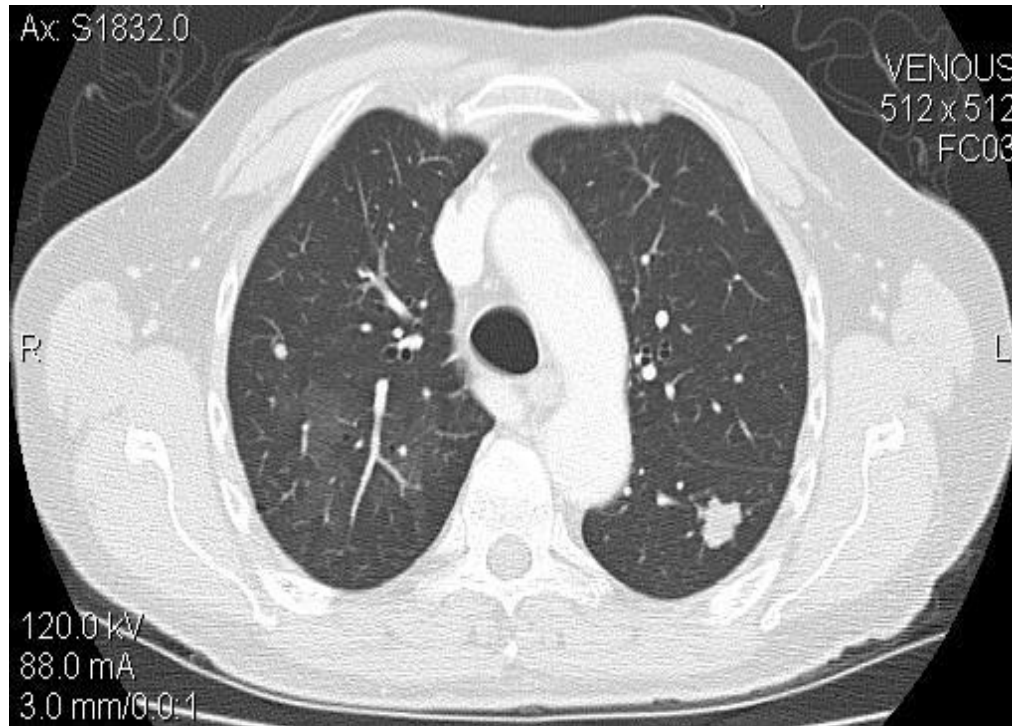






Toronto
Lung
Transplant
Program

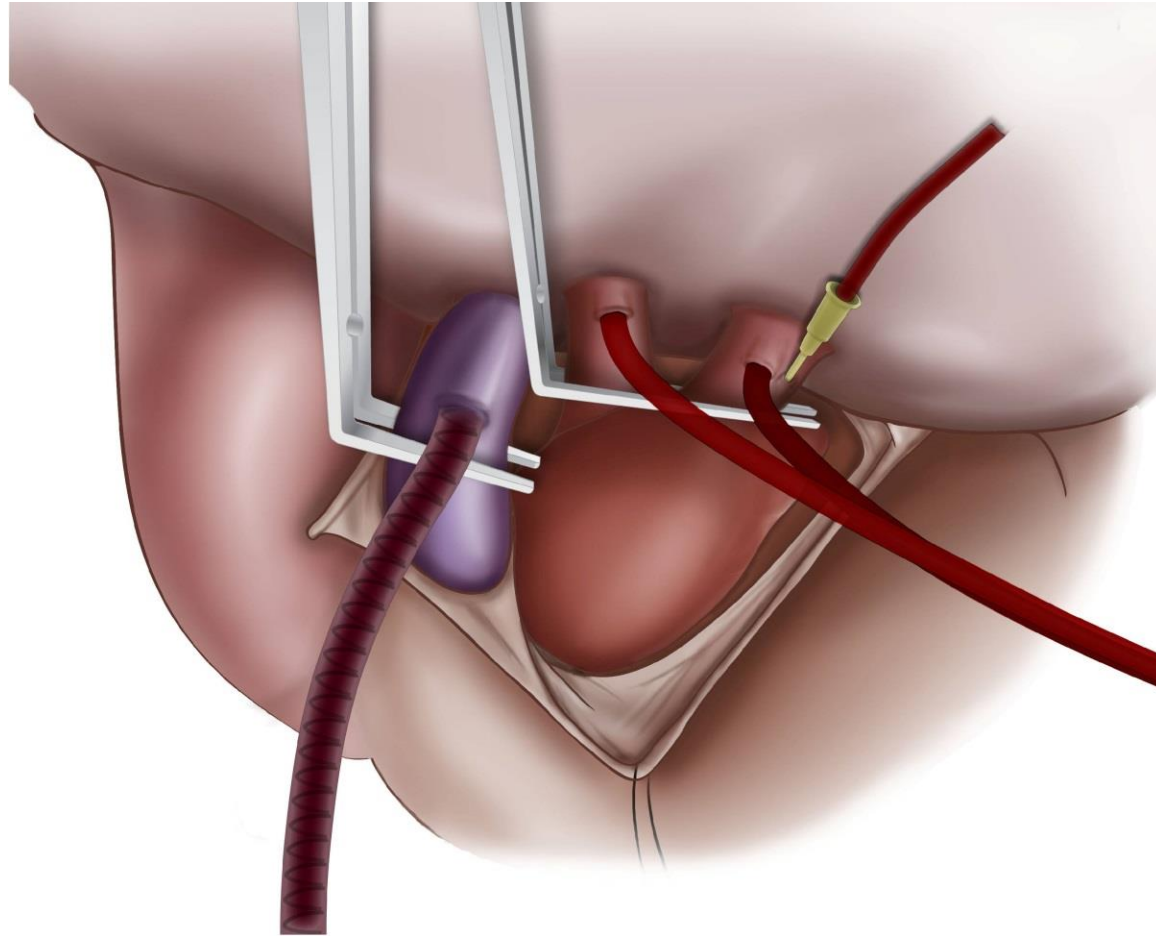
Why surgery often fails? Micrometastases





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Transplant
Program

In Vivo Lung Perfusion (IVLP)



Thoracic Surgery Latner Labs

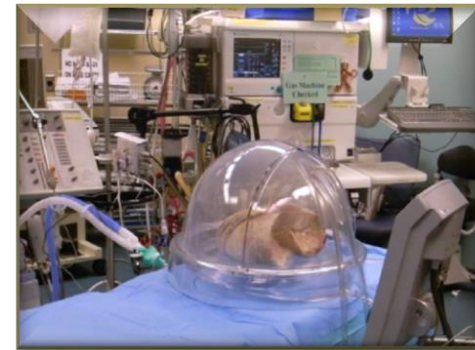
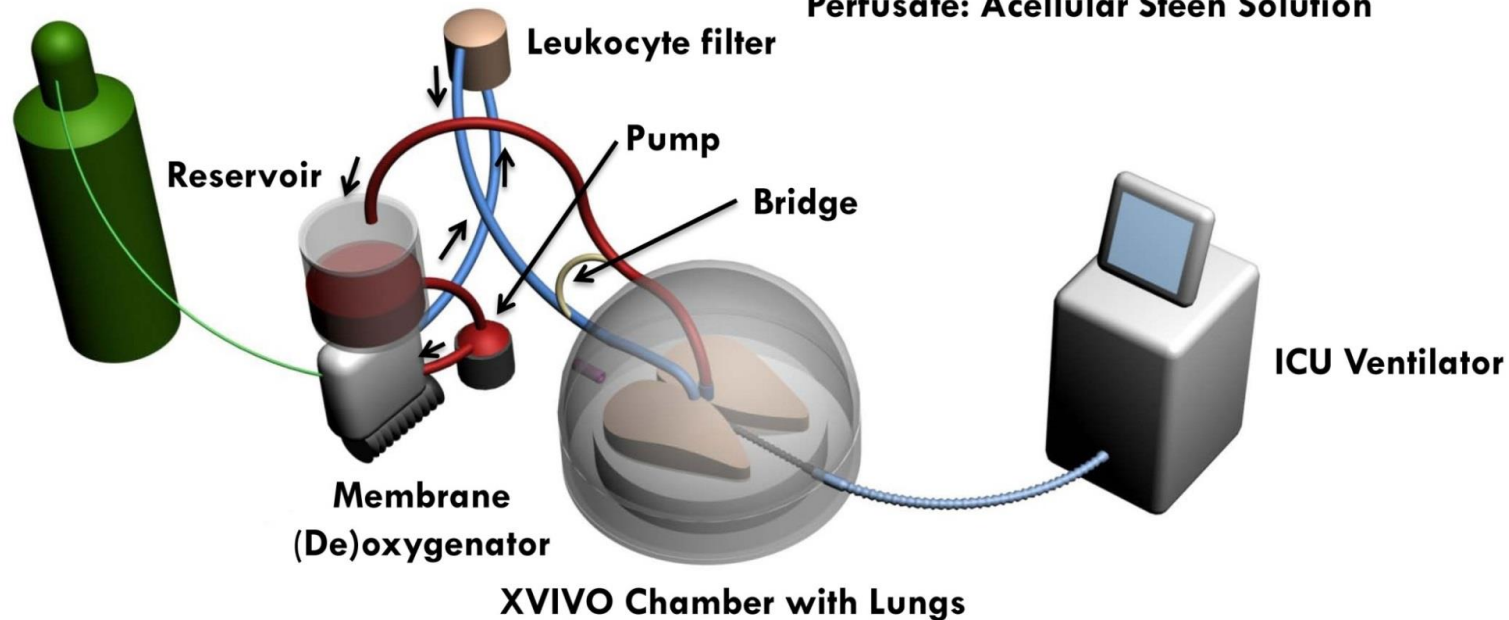


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Transplant
Program

Improved technology and better understanding of isolated lung perfusion physiology

Gas for Deoxygenation
86% N₂, 8% CO₂, 6% O₂

Red: Venous (Oxygenated) perfusate
Blue: Arterial (Deoxygenated) perfusate
Perfusate: Acellular Steen Solution

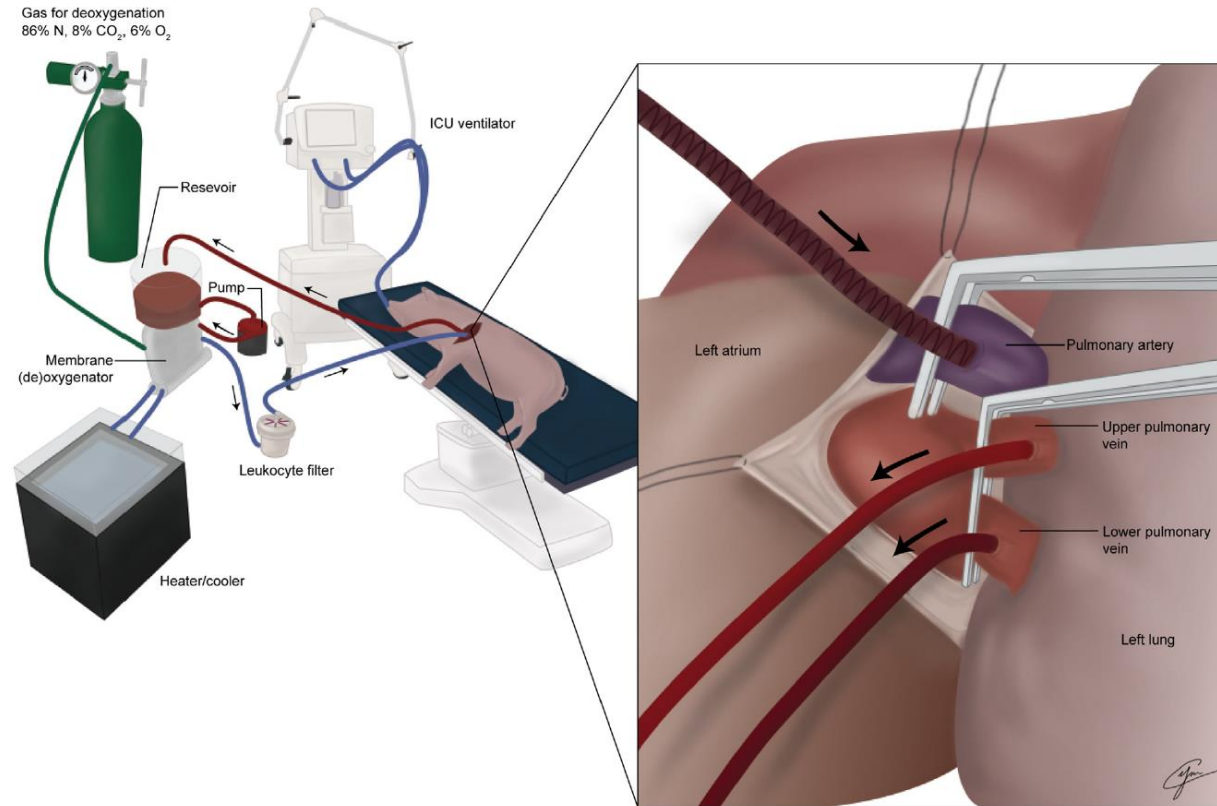
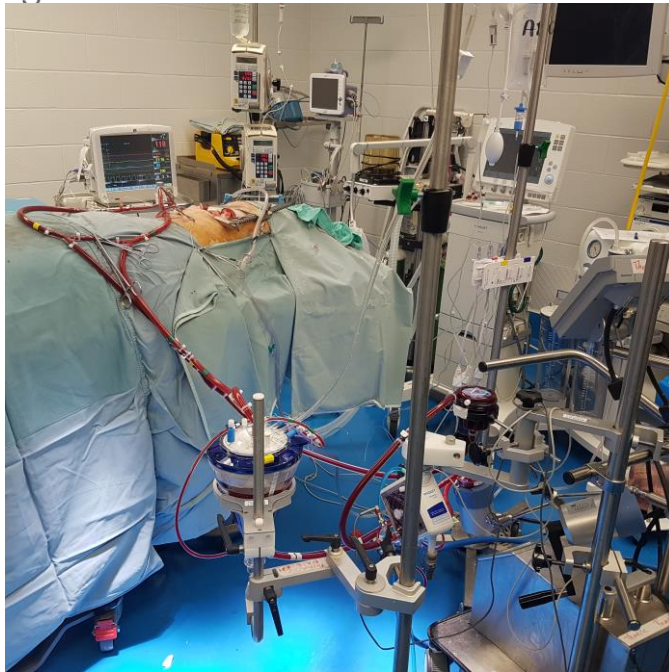






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Modified in vivo lung perfusion allows for prolonged perfusion without acute lung injury





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Surgical Oncology Insight 1 (2024) 100048



ELSEVIER

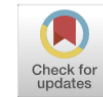
Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Surgical Oncology Insight

journal homepage: www.surgoncinsight.org



Phase I dose escalation study for In Vivo Lung Perfusion (IVLP) as an adjuvant treatment for patients with resectable pulmonary metastasis of bone or soft tissue sarcomas



Sahar A. Saddoughi^{a,c}, Jennifer Lister^a, Vinicius Schenk Michaelsen^a, Aizhou Wang^a,
Runshan Will Jiang^b, Janusz Pawliszyn^a, Shaf Keshavjee^a, Peter Slinger^d,
Juan Camilo Segura Salguero^e, Abha Gupta^f, Thomas K. Waddell^a, Albiruni Abdul Razak^f,
Marcelo Cypel^{a,*}



> [J Thorac Cardiovasc Surg.](#) 2020 Mar 21;S0022-5223(20)30635-8.
doi: [10.1016/j.jtcvs.2020.03.033](https://doi.org/10.1016/j.jtcvs.2020.03.033). Online ahead of print.

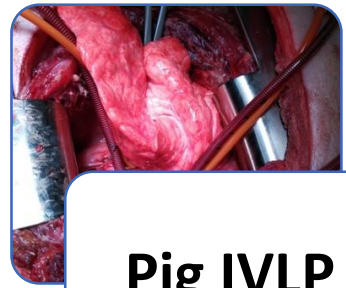
A model to assess acute and delayed lung toxicity of oxaliplatin during in vivo lung perfusion

Khaled Ramadan ¹, Bruno Gomes ¹, Mauricio Pipkin ¹, Mariola Olkowicz ², Barbara Bojko ²,
Arnaud Romeo Mbadjeu Hondjeu ³, Shaf Keshavjee ¹, Thomas Waddell ¹, Janusz Pawliszyn ²,
Marcelo Cypel ⁴

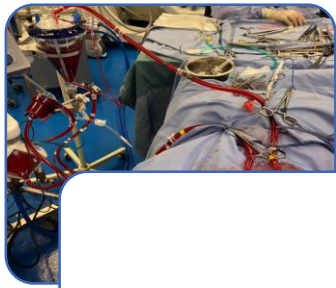
Affiliations + expand

PMID: 32354628 DOI: [10.1016/j.jtcvs.2020.03.033](https://doi.org/10.1016/j.jtcvs.2020.03.033)

IVLP Porcine Survival Study



**Pig IVLP
Surgery**



3H IVLP



**72H
Survival**



**Assessment
& Sacrifice**

**7 Animals Examined
to 72H Endpoint**

Oxaliplatin Dose Escalation

**Case 1:
0 mg/L**

**Case 2:
7.5 mg/L**

**Case 3:
10 mg/L**

**Case 4:
20 mg/L**

**Case 5:
40 mg/L**

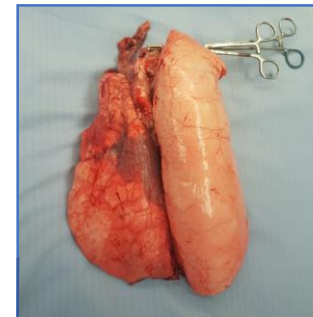
*** Case 6:
80 mg/L**

**Case 7:
40 mg/L**

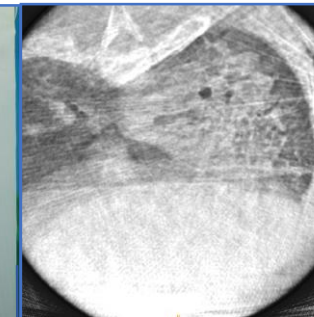
***Clinically Significant Toxicity: 80 mg/L**

Subacute pattern of lung injury

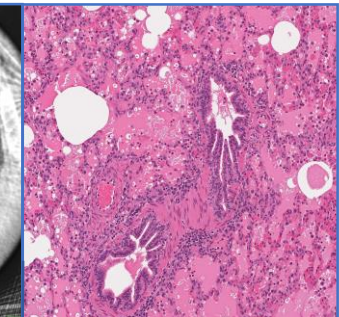
- Impaired lung function and airway mechanics
- Gross, CT & histologic findings



Gross

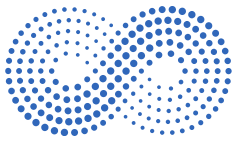


CT Imaging



Histology

Implications: Dose-limiting toxicity of 40 mg/L; Will inform development of a clinical trial.



Clinical Trial Protocol

- **Sample Size**

- N= up to 22 patients

- **Study Population**

- Colorectal carcinoma, >3 and bilateral lung metastases with absence of extrapulmonary disease (except liver mets)

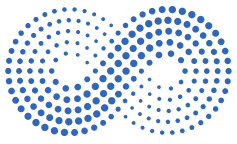
- **Dose Escalation Design**



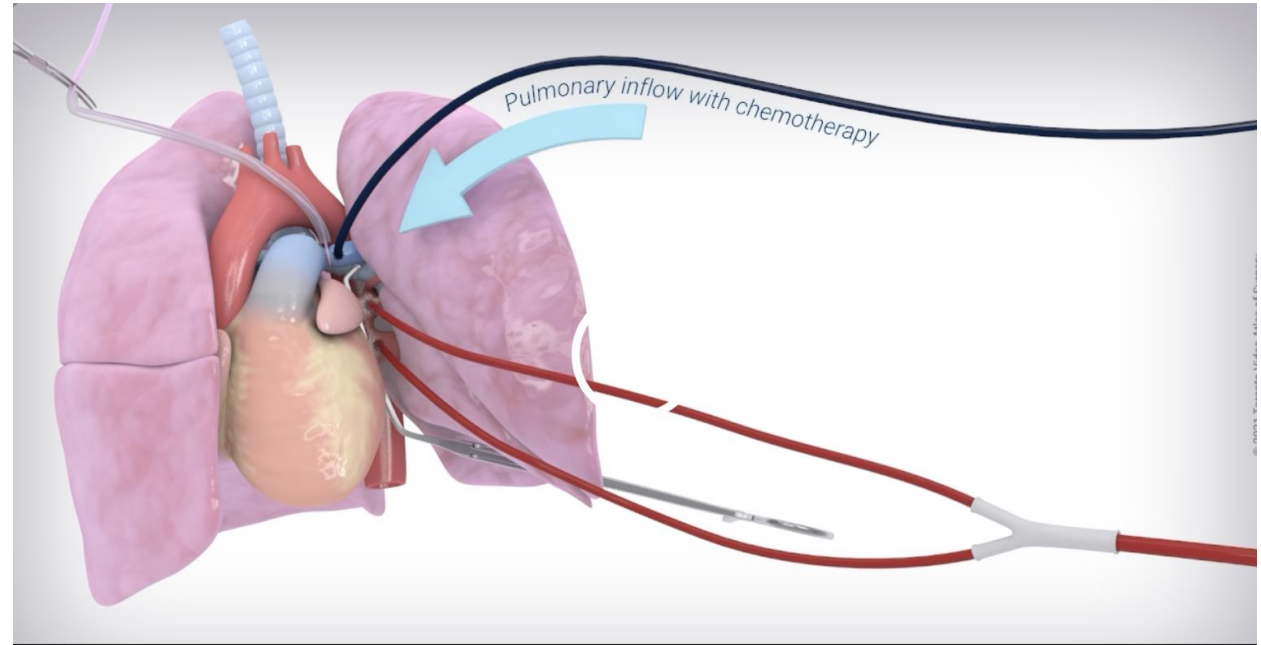
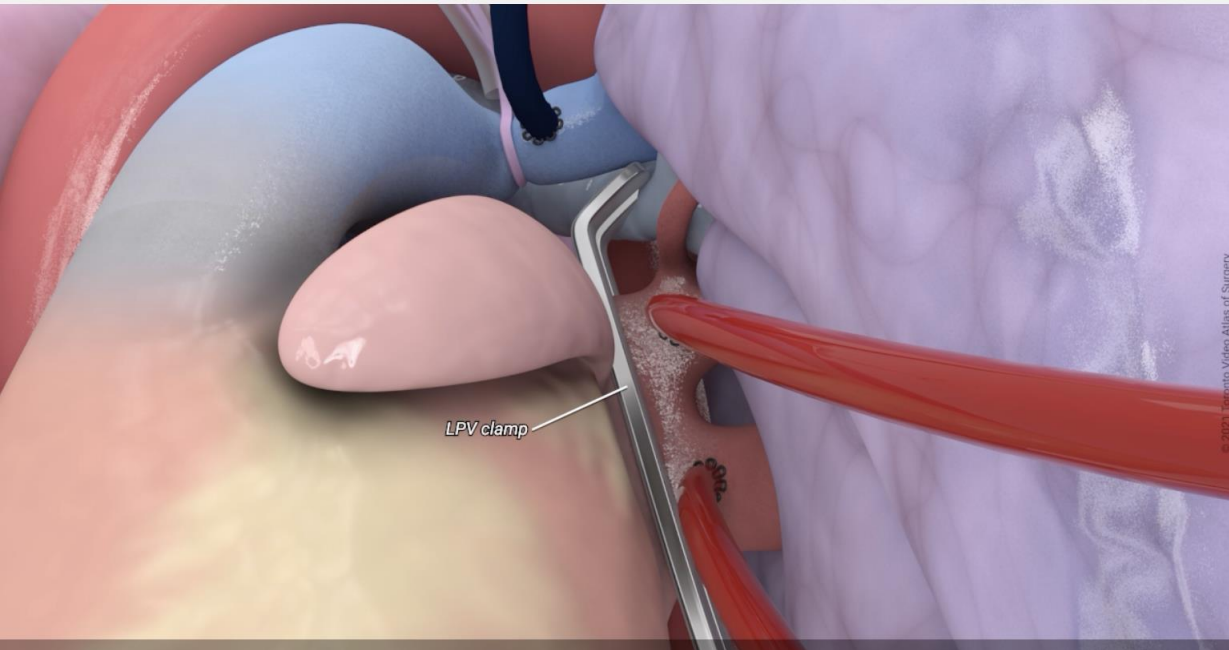
- **Primary Objectives**

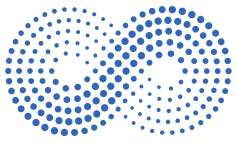
- To determine the safety of IVLP at selected dose levels
- To determine the maximal tolerated dose using a titration design

14 patients completed so far – No observed toxicity



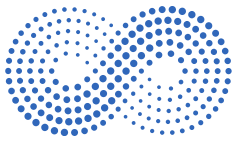
In Vivo Lung Perfusion (IVLP)





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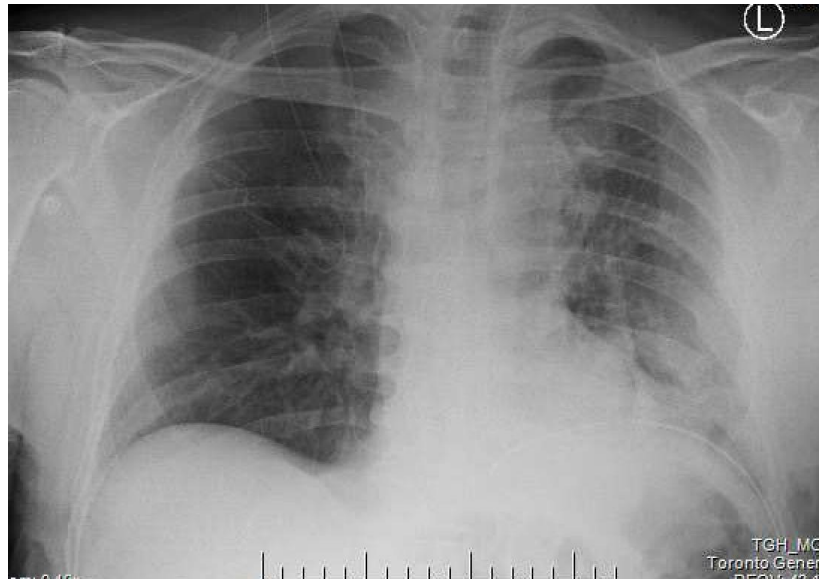


Patient example

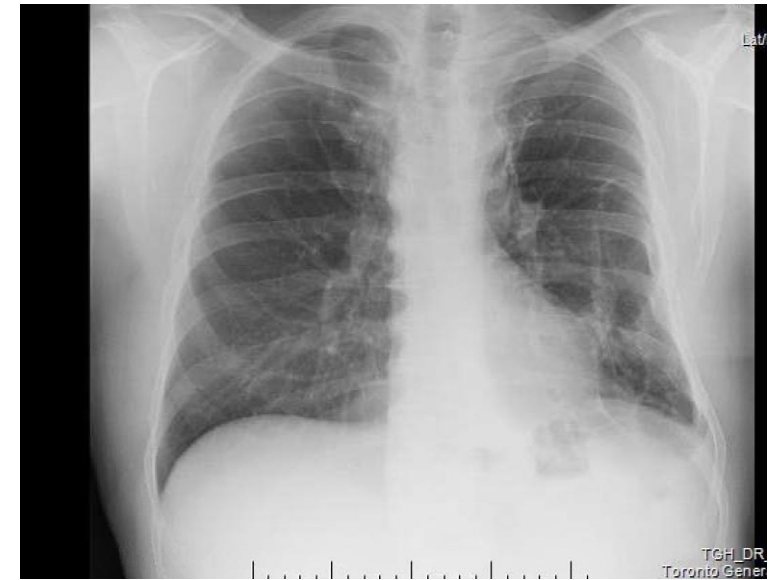
Day 1



Day 2



Day 7



Baseline Characteristics

Characteristic	N (%) or Mean (SD)
Age	45 (9)
Gender:	
• Male	8 (67%)
• Female	4 (33%)
# of lung metastases	9 (5)
Side of IVLP	
• Right	5 (42%)
• Left	7 (58%)

Groups Performed to Date:

Group 1: 5mcg/ml perfusate (n=1)

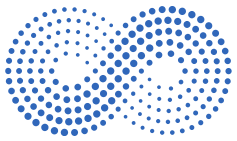
Group 2: 10mcg/ml perfusate (n=3)

Group 3: 15mcg/ml perfusate (n=3)

Group 4: 20mcg/ml perfusate (n=3)

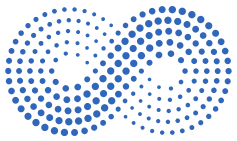
Group 5: 25mcg/ml perfusate (n=3)

Group 6: 30 mcg/ml/perfusate (n=1)



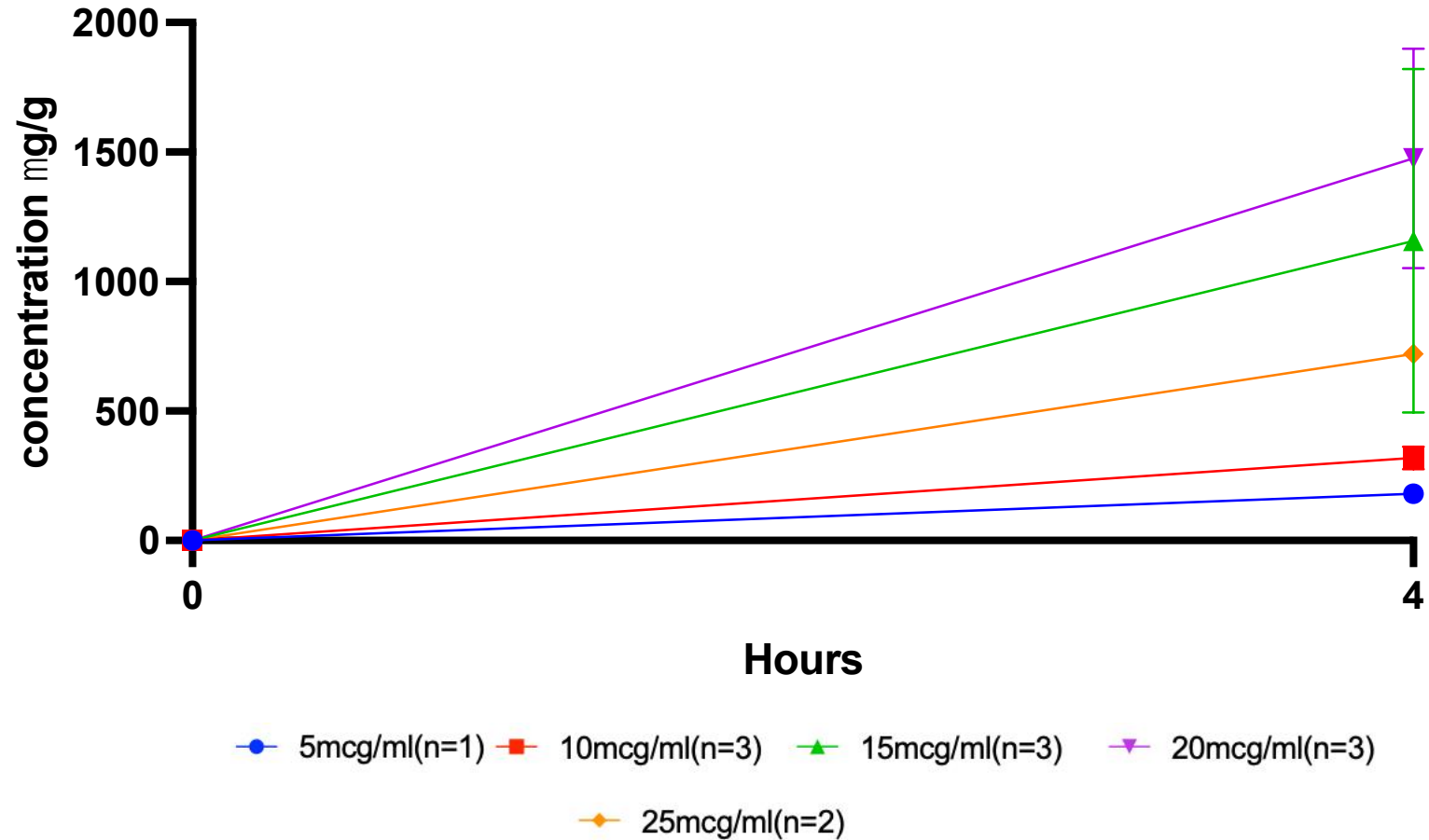
Results To Date

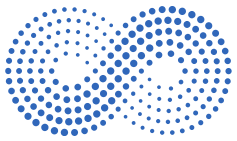
Characteristic	N (%) or Mean (SD)
Length of Stay	7.3 (2.2)
Pulmonary Edema at 72h based on CXR <ul style="list-style-type: none">• Grade 0• Grade 1• Grade 2	7 (58%) 3 (25%) 2 (17%)
Blood transfusions (# of units) <ul style="list-style-type: none">• 0• 1• 2	6 (50%) 3 (25%) 3 (25%)
Pulmonary Recurrences <ul style="list-style-type: none">• Treated Lung• Untreated Lung	3 (25%) 6 (50%)
Distant Recurrence	4 (33%)



Oxaliplatin tissue concentration

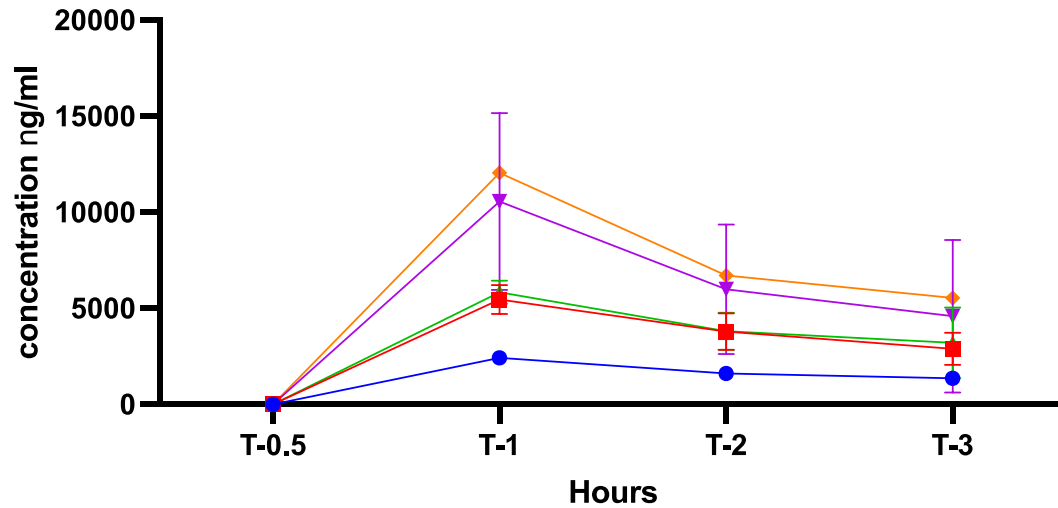
Oxaliplatin Tissue Concentration





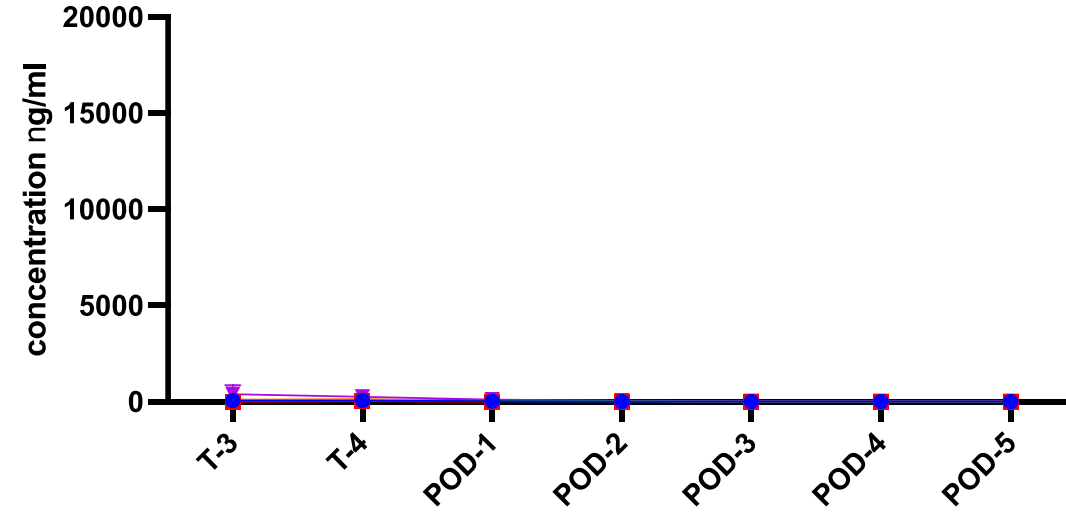
Oxaliplatin Perfusate and Plasma concentrations

Oxaliplatin Perfusate Concentration



● 5mcg/ml(n=1) ■ 10mcg/ml(n=3) ▲ 15mcg/ml(n=3) ▼ 20mcg/ml(n=3)
◆ 25mcg/ml(n=2)

Oxaliplatin Plasma Concentration





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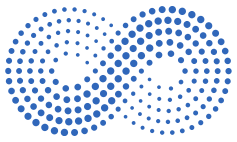
LIVES HERE



0:05 / 4:04

Scroll for details

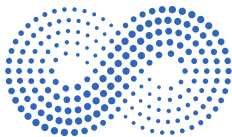




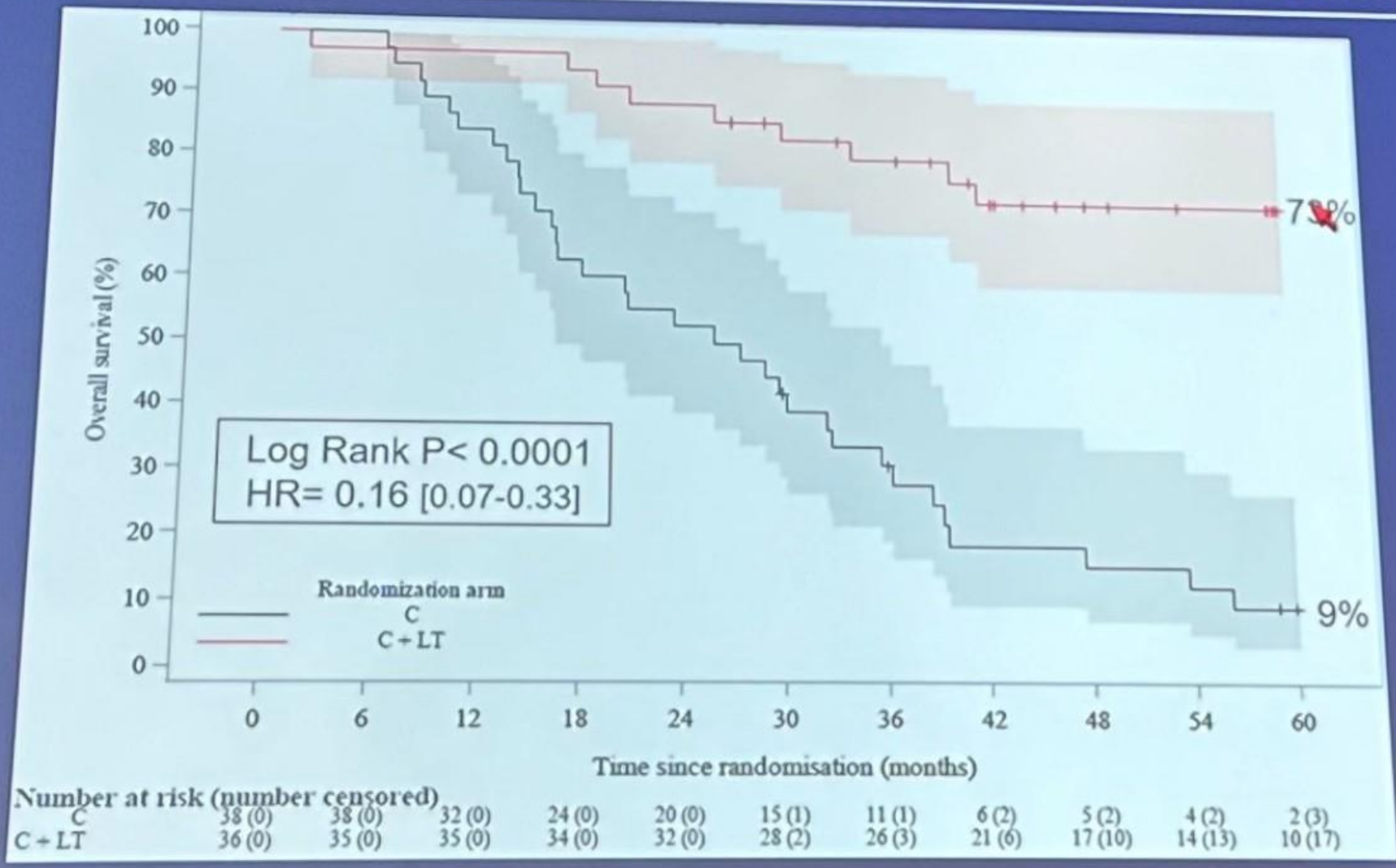
How about the unresectable patient?

Chemotherapy and liver transplantation versus chemotherapy alone in patients with definitively unresectable colorectal liver metastases: A prospective multicentric randomized trial (TRANSMET).

Rene Adam, Céline Piedvache, Laurence Chiche, Ephrem Salamé, Olivier Scatton, Victoire Granger, Michel Pierre Ducreux, Umberto Cillo, Francois Cauchy, Jean-Yves Mabrut, Chris Verslype, Laurent Coubeau, Jean Hardwigsen, Emmanuel Boleslawski, Fabrice Muscari, Jan Lerut, Lamiae Grimaldi, Francis Levi, Maité Lewin, Maximiliano Gelli; Hôpital Paul Brousse, Assistance Publique - Hôpitaux de Paris (APHP) University Paris-Saclay, Villejuif, France; Clinical Research Unit, Assistance Publique - Hôpitaux de Paris (APHP) University Paris-Saclay, Kremlin Bicêtre, France; Service de Chirurgie HPB Transplantation, Hopital Haut Leveque, Bordeaux, France; Chirurgie Digestive Hépato-biliaire et Pancréatique, Tours, France; Service de Chirurgie Hépato-Biliaire, Hôpital Pitié-Salpêtrière, Paris, France; Gastroenterology Department, Grenoble Teaching Hospital, Grenoble, France; Université Paris-Saclay, Gustave Roussy, Villejuif, France; Hepatobiliary Surgery and Liver Transplant Unit, Azienda Università di Padova, Padova, Italy; Hopital Beaujon - Assistance publique - Hôpitaux de Paris (APHP), Clichy, France; University Hospital Lyon, Lyon, France; University Hospitals Leuven, Leuven, Belgium; Université de Louvain, Louvain, Belgium; Assistance Publique – Hôpitaux de Marseille, Marseille, France; Department of Digestive Surgery and Transplantation, University Hospital of Lille, Lille, France; Hôpital Rangueil CHU Toulouse, Toulouse, France; Université Catholique de Louvain, Louvain, Belgium; UPR Chronotherapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France; Assistance Publique - Hôpitaux de Paris (APHP) University Paris-Saclay, Villejuif, France



TransMet Trial : Primary Endpoint 5-Yr OS (Per Protocol)



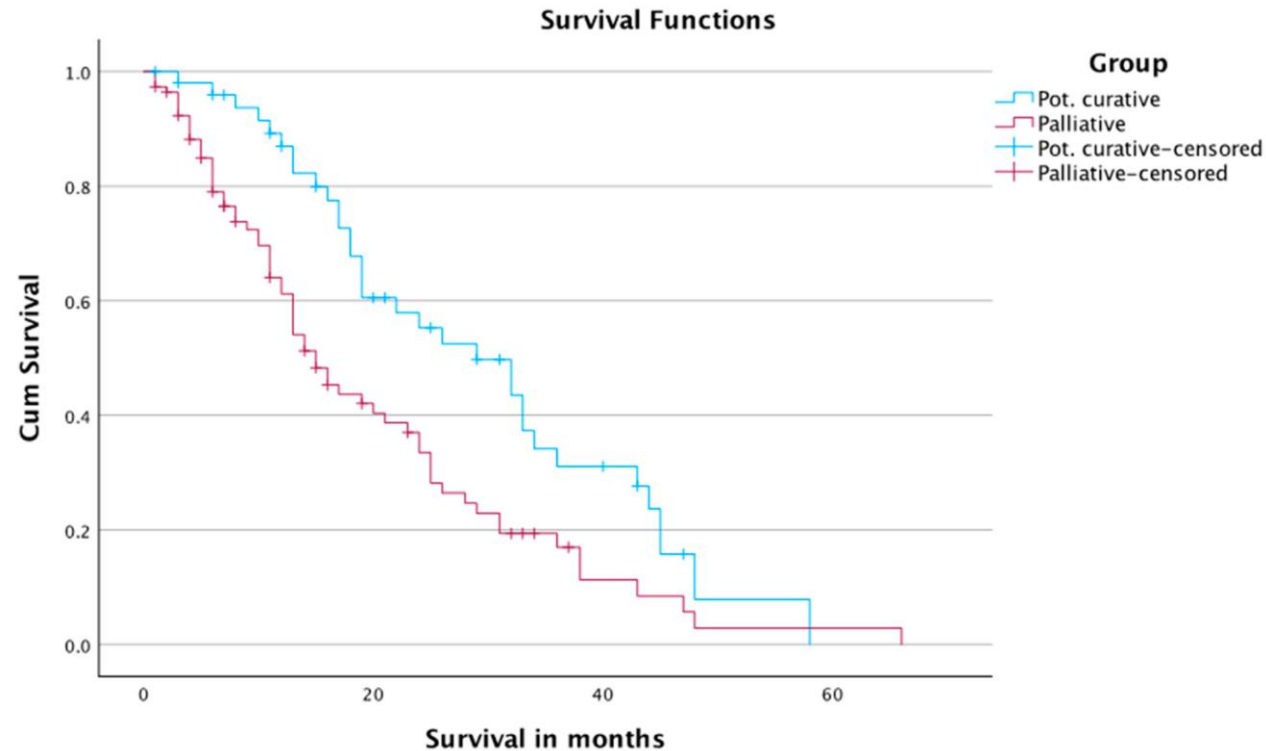
Transvenous Pulmonary Chemoembolization and Optional Microwave Ablation for Colorectal Lung Metastases

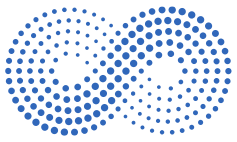
by Thomas J. Vogl *  , Lars Hammann and Hamzah Adwan

Department of Diagnostic and Interventional Radiology, University Hospital, Goethe University Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

* Author to whom correspondence should be addressed.

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