



# What's (old and) new? Lung metastases

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# What's new?

## Lung metastases

- history - controversy - evidence
- retrospective data
- how to do it?
- treatment algorithm
- how to improve local control?





# What's new?

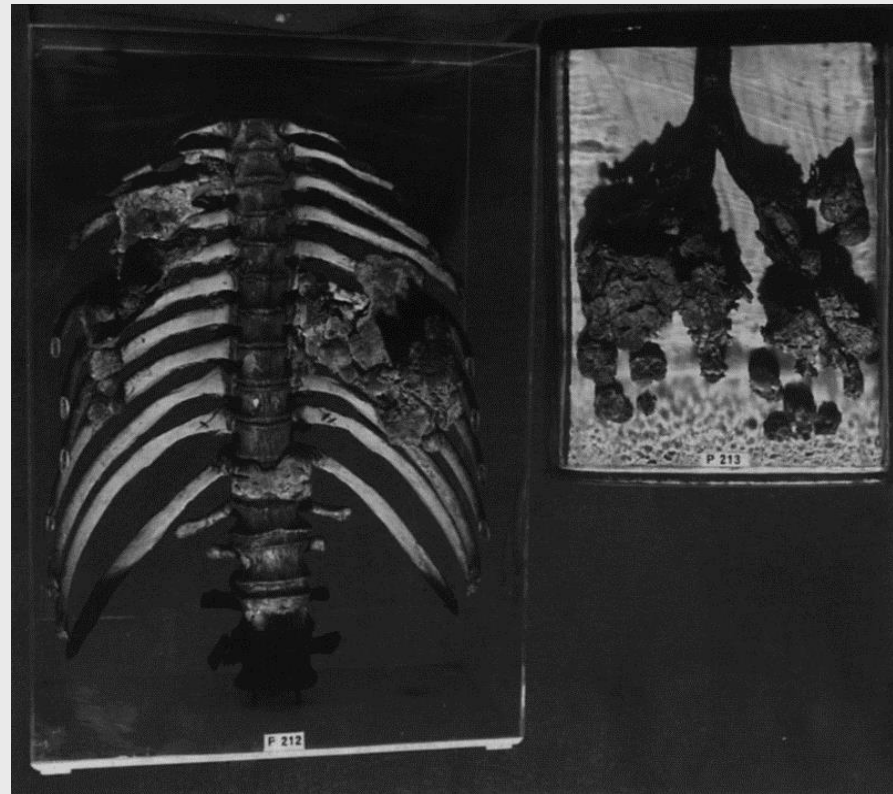
## Lung metastases

- **history - controversy - evidence**
- retrospective data
- how to do it?
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- how to improve local control?



# Surgery for pulmonary metastases

1786 J. Hunter





# Surgery for pulmonary metastases

## History

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- |      |                          |  |
|------|--------------------------|--|
| 1786 | J. Hunter                | case of pulm. mets                         |
| 1927 | J. Divis                 | resection pulmonary mets                   |
| 1939 | J. Barney - E. Churchill | lobectomy - metastasis kidney: nephrectomy |
| 1965 | N. Thomford              | 205 patients<br>5-year survival 30.3 %     |





# Surgery for pulmonary metastases

- Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness?  
[T. Treasure et al. Thorax 2014; 69:946-9](#)
- Pulmonary metastasectomy: a call for better data collection, presentation and analysis.  
[F. Fiorentino, T. Treasure. Future Oncol 2015; 11 \(2 Suppl\):19-23](#)
- Pulmonary metastasectomy: where is the evidence?  
[F. Macbeth, T. Treasure. J Thorac Oncol 2015; 10:e13-14](#)





# Surgery for pulmonary metastases

- retrospective case series
- selection bias
- no level 1 evidence, no control group
- “There is reason *to believe* that any perceived survival benefit may simply be due to patient selection. This is an insecure foundation of which to justify ablative therapies.”

F. Macbeth, T. Treasure. *J Thorac Oncol* 2015; 10:e13-14





# Surgery for pulmonary metastases

- no large randomized trials to prove survival benefit compared to conservative treatment
- also for thymoma, mesothelioma, even early stage lung cancer!
- N2 disease: 3 large RCT; still highly controversial
- reverse statement not proven:  
*absence of evidence  $\neq$  evidence of absence*

P. Van Schil. J Thorac Oncol 2015; 10:e14-15







# Current status of pulmonary metastasectomy - Review

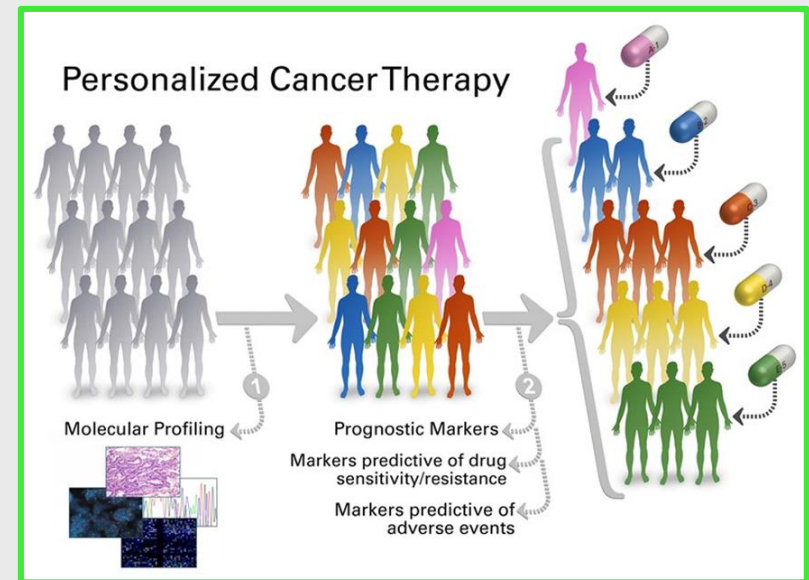
➤ 30% of all cancer patients will develop lung metastases

➤ 5-year survival rates

untreated	5 - 10%
resected	30 - 50%

*selection bias ??*

Hornbech K. Eur J Cardiothorac Surg  
2011; 39:955-62





# Surgery for pulmonary metastases

## Selection criteria

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- able to withstand the operation planned (cardiac, functional evaluation)
- *complete* resection of all pulmonary mets
- primary tumor and extrapulmonary mets must be controlled or controllable
- no *better* treatment available offering the same chance of cure or superior palliation

Harvey JC. Chest Surg Clin North Am 1994; 4:55



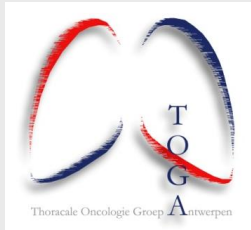


# What's new?

## Lung metastases

- history - controversy - evidence
- **retrospective data**
- how to do it?
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## GENERAL THORACIC SURGERY

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### LONG-TERM RESULTS OF LUNG METASTASECTOMY: PROGNOSTIC ANALYSES BASED ON 5206 CASES

The International Registry of Lung Metastases\*

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*Objectives:* The International Registry of Lung Metastases was established in 1991 to assess the long-term results of pulmonary metastasectomy. *Methods:* The Registry has accrued 5206 cases of lung metastasectomy, from 18 departments of thoracic surgery in Europe ( $n = 13$ ), the United States ( $n = 4$ ) and Canada ( $n = 1$ ). Of these patients, 4572 (88%) underwent complete surgical resection. The primary tumor was epithelial in 2260 cases, sarcoma in 2173, germ cell in 363, and melanoma in 328. The disease-free interval was 0 to 11 months in 2199 cases, 12 to 35 months in 1857, and more than 36 months in 1620. Single metastases accounted for 2383 cases and multiple lesions for 2726. Mean follow-up was 46 months. Analysis was performed by Kaplan-Meier estimates of survival, relative risks of death, and multivariate Cox model. *Results:* The actuarial survival after complete metastasectomy was 36% at 5 years, 26% at 10 years, and 22% at 15 years (median 35 months); the corresponding values for incomplete resection were 13% at 5 years and 7% at 10 years (median 15 months). Among complete resections, the 5-year survival was 33% for patients with a disease-free interval of 0 to 11 months and 45% for those with a disease-free interval of more than 36 months; 43% for single lesions and 27% for four or more lesions. Multivariate analysis showed a better



# Surgery for pulmonary metastases International Registry

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- 5206 cases of lung metastasectomy
- mean follow-up : 46 months
- complete resection : 4572 (88 %)
- male : 2392 (56 %)    female : 2274 (44 %)
- mean age : 44 years (range 2-93)

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases International Registry

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- primary tumor

epithelial	2260	43%
sarcoma	2173	42%
germ cell	363	7%
melanoma	328	6%

- DFI

0-11 mos.	1603	31%
12-35	1857	36%
> 36	1620	31%

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases International Registry

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- single metastasis                      2383                      46%
- multiple                                      2726                      52%
  - 4 or more                                      1353                      26%
  - 10 or more                                      457                      9%
- hilar or mediastinal nodes : 239 (5%)

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases International Registry

overall mortality 1.0 %

	5 - year	10 - year	median
complete	36%	26%	35 mos
incomplete	13%	7%	15 mos
DFI 0-11 mos	33%	27%	29 mos
12 - 35	31%	22%	30 mos
> 36	45%	29%	49 mos







# Surgery for pulmonary metastases International Registry

	5 - year	10 - year	median
single	43%	31%	43 mos
2 or 3	34%	24%	31 mos
4 or more	27%	19%	27 mos

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases International Registry

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- multivariate analysis complete resection
- significant prognostic factors
  - primary tumor type (germ cell, Wilms)
  - DFI (>36 mos)
  - number of mets (single)

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases International Registry

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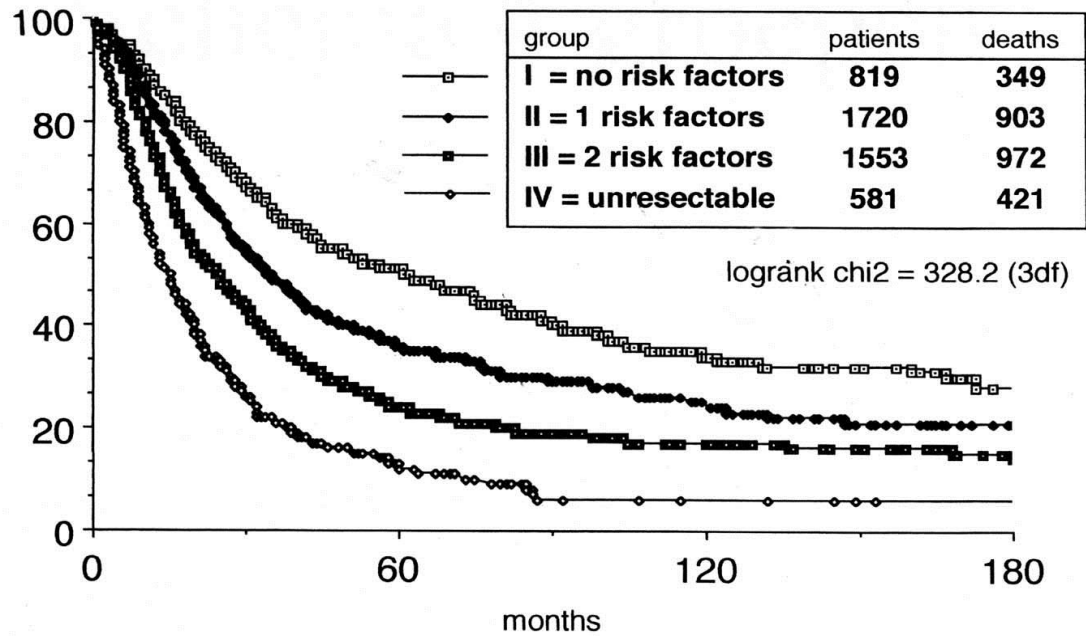
## *prognostic groups*

			<u>MST (mos.)</u>
group	I	single and DFI > 35 mos.	61
	II	single or DFI > 35 mos.	34
	III	multiple, DFI < 36 mos.	24
	IV	incomplete resection	14





# Surgery for pulmonary metastases International Registry



Patients at risk:

Group	0	60	120	180
I	198	65	20	20
II	296	85	30	30
III	189	60	18	18
IV	31	5	1	1

Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49



# Surgery for pulmonary metastases

## Lung mets: recent series

- 575 pts                      708 pulmonary metastasectomies
- retrospective review 1998 – 2008
- open resection 83.3%      DFI 46.6 months
- results:
  - 5-year survival complete resection 46%
  - multivariate analysis: complete resection  
germ cell tumors  
DFI  $\geq$  36 months
- not significant: n mets, n of metastasectomies



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# Surgery for pulmonary metastases

## International Registry

### Surgical approach

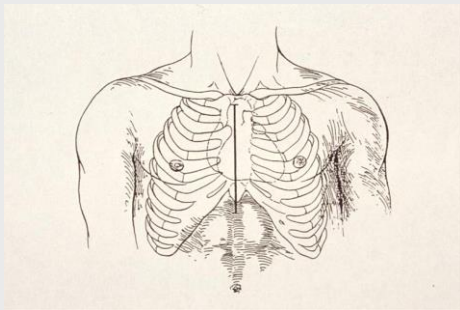
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• unilateral thoracotomy	3111	58%
• bilateral or staged	576	11%
• median sternotomy	1415	27%
• VATS	93	2 %

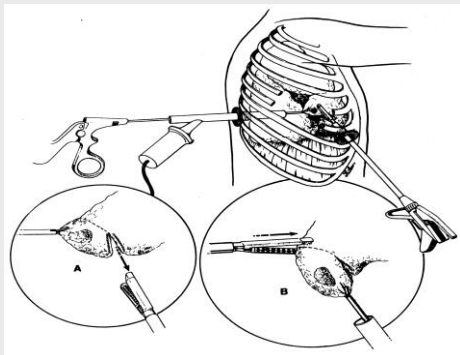
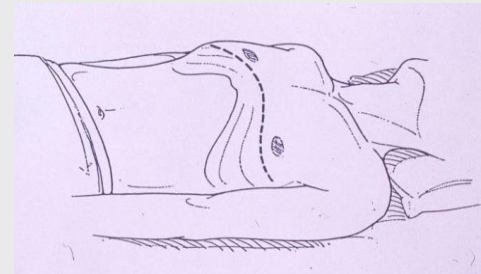
Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49



# Surgery for pulmonary metastases



median sternotomy  
thoracotomy  
“clam shell” incision



thoracoscopy (VATS)  
robotic da Vinci® system







# Surgery for pulmonary metastases International Registry

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- maximal resected volume

sublobar	3922	76%
(bi)lobectomy	1109	21%
pneumonectomy	133	3%
- extended resection

chest wall, diaphragm, LN	446	9%
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Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49





# Surgery for pulmonary metastases

## Controversies

- ✓ unilateral versus bilateral exploration
- ✓ simultaneous versus staged resections
- ✓ open versus closed



# Surgery for pulmonary metastases

## Role of VATS

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- accuracy of VATS peripheral lung mets
- 28 pts CT scan :  $\leq 3$  solitary mets  
 $\leq 3$  cm, peripheral nodules
- VATS + confirmatory thoracotomy
- VATS :

10	technically impossible
1	carcinoid
17	confirmatory thoracotomy

Mutsaerts EL. Ann Thorac Surg 2001; 72 : 230-3





# Surgery for pulmonary metastases

## Role of VATS

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- confirmatory thoracotomy 17
  - complete resection by VATS 12
  - residual disease 5
- success rate : 1 lesion 11/12 correct
  - > 1 lesion 1/5 correct
- VATS : solitary pulmonary metastasis
  - $\leq 3$  cm, peripheral nodule

Mutsaerts EL. Ann Thorac Surg 2001; 72 : 230-3





# Surgery for pulmonary metastases

## Role of VATS *observer blinded study*

- oligometastatic pulmonary disease
- VATS + thoracotomy (different team)
- 89 pts CT 140 suspicious nodules
- VATS 122 nodules palpated (87%)
- thoracotomy: 67 additional nodules  
22 mets (33%) 43 benign (64%) 2 lung cancers (3%)
- VATS : inadequate to resect all pulmonary metastases

Eckardt J, Licht P. *Ann Thorac Surg* 2014; 98:466-70





# Surgery for pulmonary metastases

## Lymph node dissection

- ✓ complete mediastinal lymph node dissection advised
- ✓ 883 pts resection lung metastases
  - 70 pts (7.9%) complete lymphadenectomy
  - 20 + LN (28.6%)      9 N1    8 N2    3 N1+2
- ✓ 3-year survival
  - LN    69%
  - + LN    38 %     $p < .001$



# What's new?

## Lung metastases

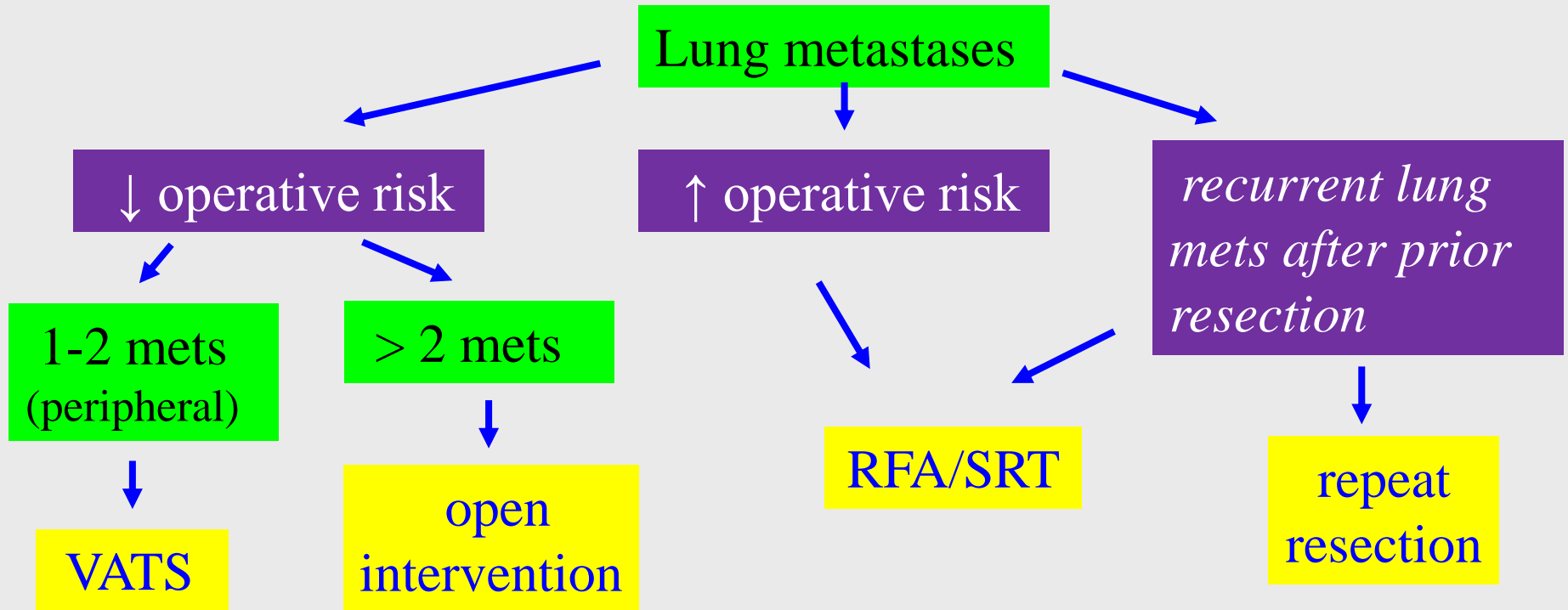
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# Surgery for pulmonary metastases

## Treatment algorithm







# What's new?

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# Surgery for pulmonary metastases

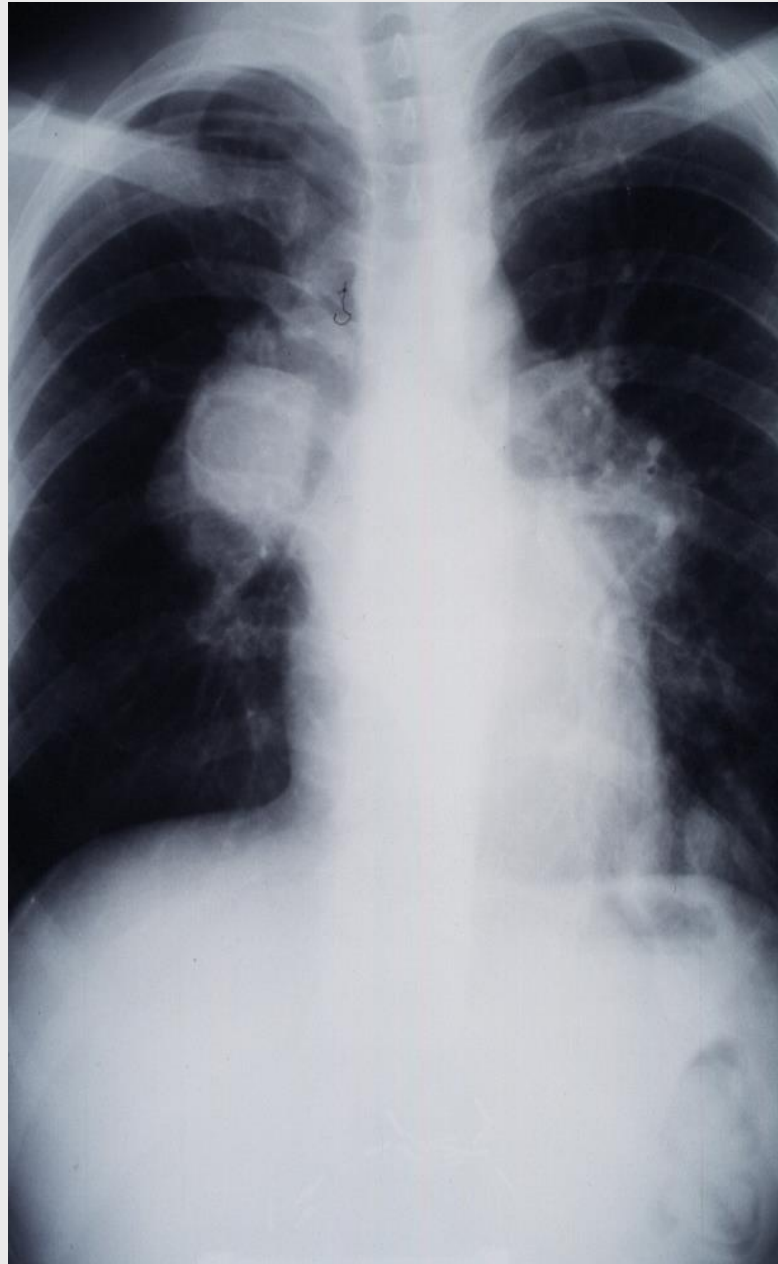
## Case report

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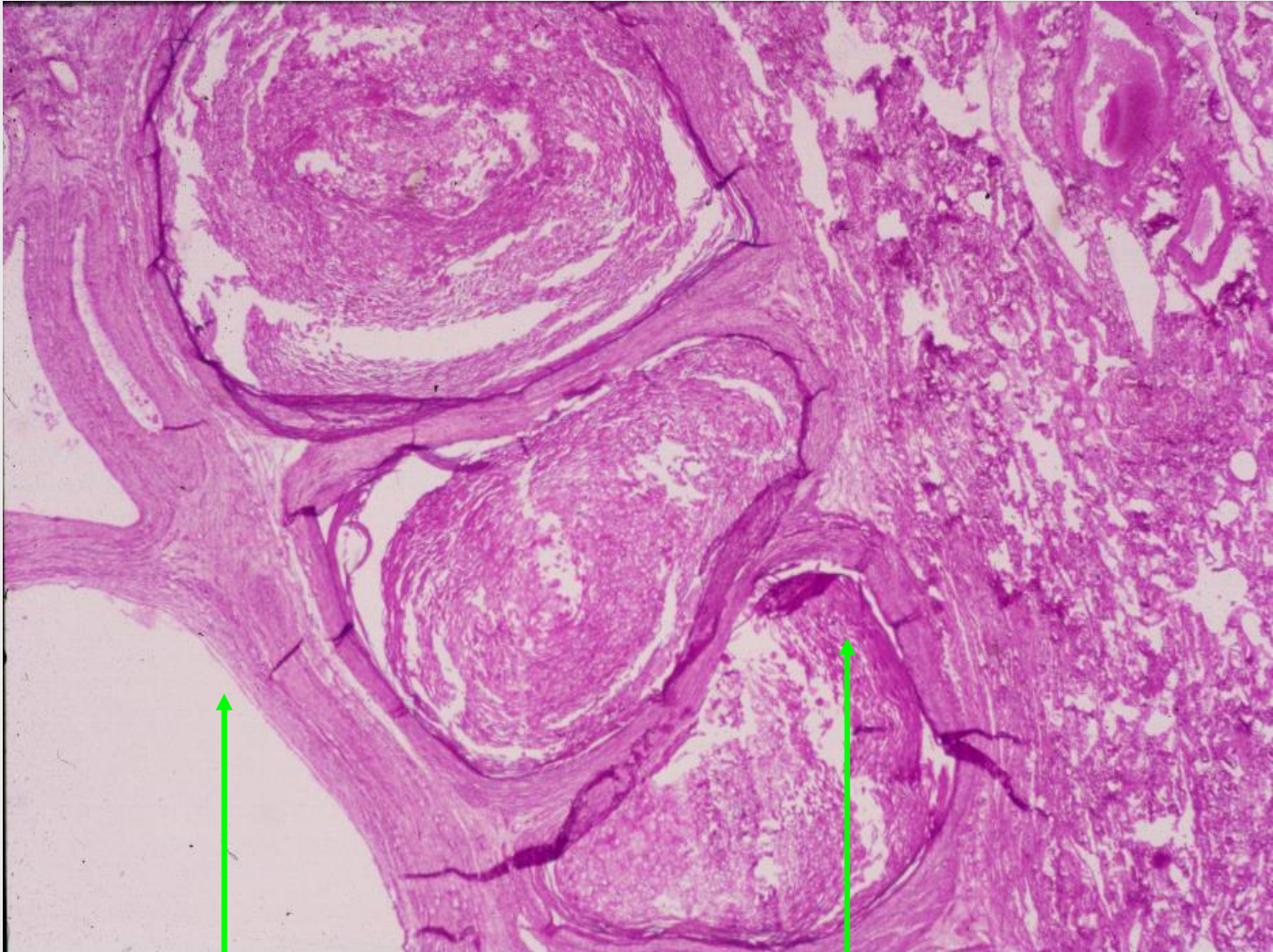
° 27-07-62 ♂

- 1983 orchietomy L + retroperit. lymphadenectomy (teratocarcinoma)
- 1985 shortness of breath  
pulmonary mets; chemotherapy
- 1986 L thoracotomy (mature teratoma)









respiratory epithelium

squamous epithelium



# Surgery for pulmonary metastases

## Case report

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alphafetoprotein :	4/90	1.4 ng/ml
	5/94	5220 ng/ml

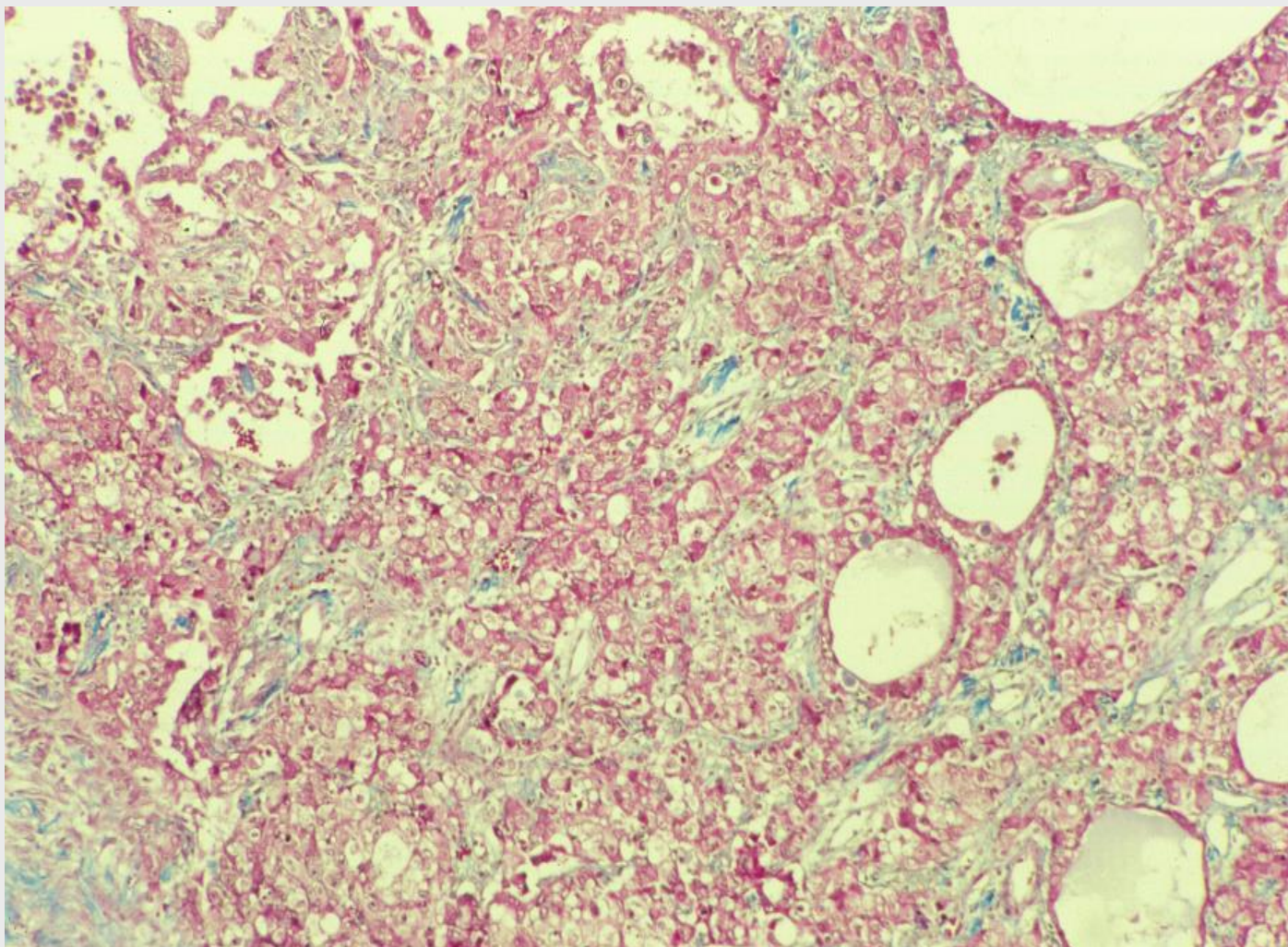
- 3 cycles chemotherapy (2 BEP, 1 VIP)
- 7/94 R pneumonectomy
  - metastases RUL
  - mature teratoma subcarinal



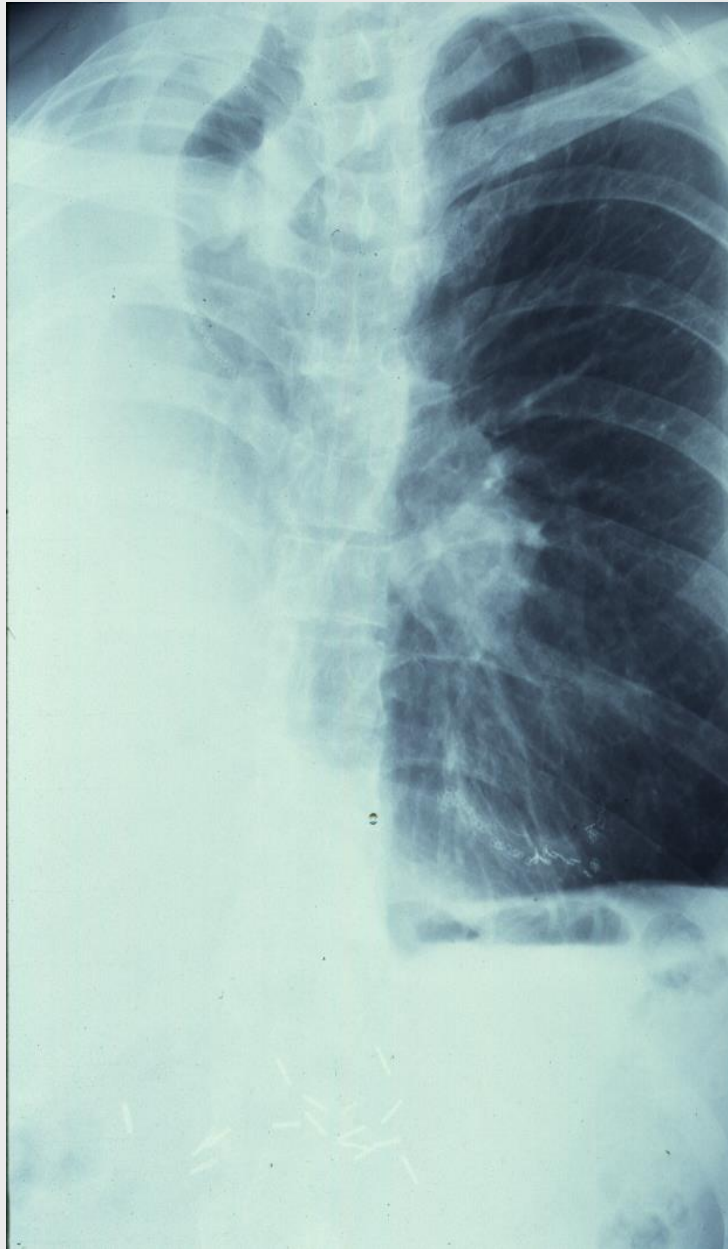




persisting embryonal carcinoma RUL







# Lung metastasectomy - recurrences

Relapse	Epithelial Sarcoma Melanoma		
	%	%	%
Single Intrathoracic	5	21	
Multiple Intrathoracic	45	36	20
Intra-and Extrathoracic	17	7	40
Extrathoracic	33	36	40

**Table II. Relapse after metastasectomy**

Relapse	Epithelial		Sarcoma		Germ cell		Melanoma	
	No.	%	No.	%	No.	%	No.	%
All sites	917	12	1218	16	84		180	
Single intrathoracic	111	12	191	16	18	21	14	8
Multiple intrathoracic	291	32	607	50	30	36	34	19
Extrathoracic	515	56	420	34	36	43	132	73
Second metastasectomy	260	28	642	53	34	40	28	16



# Surgery for pulmonary metastases

## Alternative treatments

### Optimizing systemic + local control

- induction or adjuvant chemotherapy
- alternative techniques: SBRT, RFA
- biological techniques (inhaled interleukins)
- molecular or genetic therapy
- isolated lung perfusion (high local drug concentration)
- regional drug delivery (pulm.art. blood flow occlusion)





# Isolated Lung Perfusion

- pulmonary metastases (PM)
  - CRC: 5-15%
  - sarcoma: 20-50%
- high pulmonary recurrence (up to 66%) due to undetected micrometastases
- surgical resection limited due to decrease in lung function
- systemic chemotherapy limited due to decrease in lung function





# Isolated Lung Perfusion

## Phase II clinical trial

A multicentre phase II clinical trial of isolated lung perfusion with melphalan in 107 patients with resectable lung metastases





# Isolated Lung Perfusion

## Method

- Lung isolation
  - Heparinisation
  - Cannulation of pulmonary artery and two pulmonary veins
  - Central clamping
  - Snaring main bronchus
- Centrifugal pump and closed circuit
- 45 mg melphalan at 37 °C for 30 minutes followed by a 5-minute washout





# Phase II trial

## Methods

- Pulmonary metastasectomy with lymphadenectomy
- Postoperative complications were scored using the extended Clavien-Dindo classification
- Lung function was measured preoperatively and at 1, 3, 6, 9 and 12 months
- Follow-up CT scans were performed to evaluate local and distant disease progression





# Phase II trial

## Goals

- evaluation
  - local control:
    - time to local pulmonary progression (TTLPP)
    - pulmonary progression-free survival (PPFS)
  - distant control:
    - time to progression (TTP)
    - disease-free survival (DFS)
  - overall survival:
    - median survival time (MST)
    - rate of overall survival
- confirm
  - safety
  - feasibility





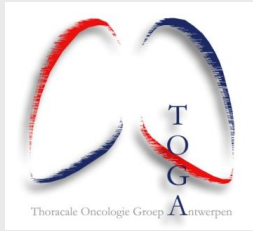


# Phase II trial

## Patients

- 107 patients; 136 procedures
  - CRC: n=57
  - sarcoma: n=50
- 29 bilateral procedures
- male – female: 63-44
- mean age: 51 years (range: 19-78)
- mean DFI: 18 months (range: 0-168)
- median of 2 active metastases were found on pathology





# Phase II trial

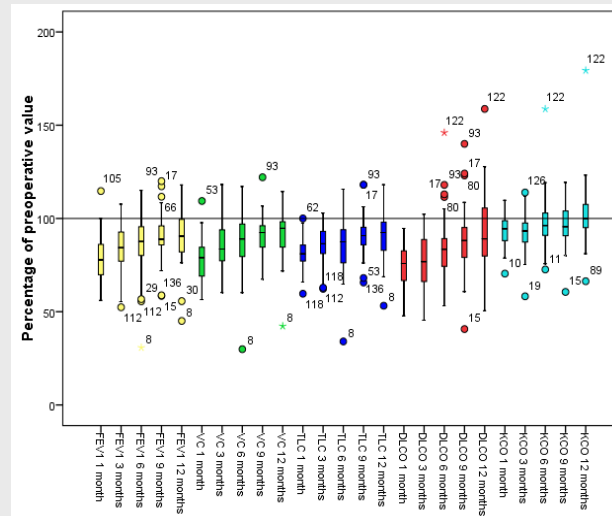
## Results

- safety:
  - no perioperative mortality
  - recovery of lung function within 12 months
  - 12 (8.8%) severe complications

**Table 1: LUNG FUNCTION 12 MONTHS AFTER ILUP**

	Mean % of preoperative value	SD
FEV1	91.06	16.11
VC	91.72	14.16
TLC	91.14	13.78
DLCO	93.24	2.50
KCO	103.61	19.28

ILUP: Isolated lung perfusion; SD: Standard deviation; FEV1: Forced expiratory volume in 1 second; VC: Vital capacity; TLC: Total lung capacity; DLCO: Diffusing capacity; KCO: DLCO/VA



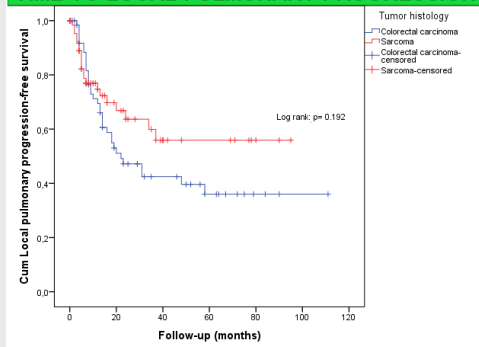
**Table 2: SEVERE COMPLICATIONS**

	Complication	Treatment	No. of pts
Grade IIIa	Atelectasis	Bronchoscopy	3
	Pneumonia	Bronchoscopy	2
	Pneumothorax	New chest tube	1
	Pleural effusion	New chest tube	1
Grade IIIb	Fibrotic lung	Pleural puncture, Diuretics	1
	Postoperative bleeding	Reoperation	1
Grade IV	Chest tube sutured to skin	Reoperation	1
	ARDS	ICU admission	1
Grade IVa	Peroperative anaphylactic shock	Fluids, medication, ICU admission postoperatively	1

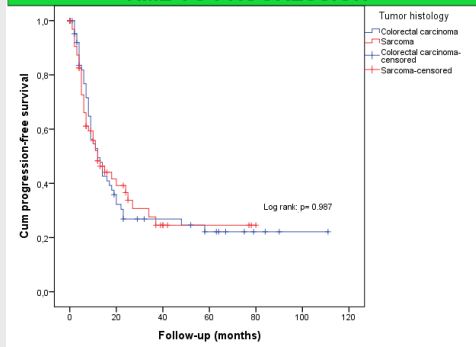
# Phase II trial

## Results

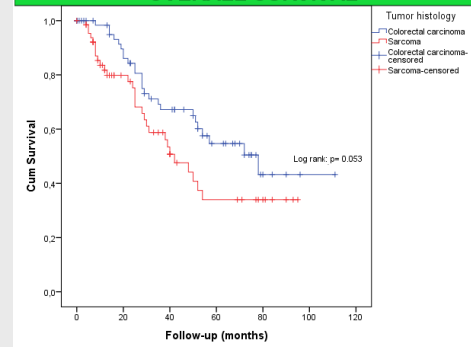
**TIME TO LOCAL PULMONARY PROGRESSION**



**TIME TO PROGRESSION**



**OVERALL SURVIVAL**



**Table 3: SURVIVAL DATA ACCORDING TO TUMOR HISTOLOGY**

	Median TTLPP <sup>1</sup> (95% CI)	3-year PPFS	Median TTP <sup>1</sup> (95% CI)	3-year DFS	MST <sup>1</sup> (95% CI)	5-year OS
CRC	22 (10-34)	42 ± 7%	12 (7-17)	27 ± 6%	78 (35-121)	57 ± 9%
Sarcoma	NR	60 ± 8%	12 (7-18)	28 ± 7%	42 (29-55)	34 ± 8%
Overall	34 (4-64)	50 ± 5%	12 (9-15)	27 ± 4%	50 (36-64)	46 ± 5%

<sup>1</sup> Time in months

MST: median survival time; OS: overall survival; TTP: time to progression; TTLPP: time to local pulmonary progression; DFS: disease-free survival; CRC: colorectal carcinoma; NR: not reached

**Table 4: LOCATION OF FIRST RECURRENCE**

	Ipsilateral lung	Contralateral lung	Local (primary)	Other	Multiple sites
No. of patients	41	18	5	13	8
% of total patients	30	13	4	10	6
% of total recurrence	48	21	6	15	9

# Phase II trial

## Results

**Table 5:** SURVIVAL DATA FOR SPREAD OF DISEASE ACCORDING TO TUMOR HISTOLOGY

	Median TTLPP <sup>1</sup> (95% CI)	3-year PPFS	Median TTP <sup>1</sup> (95% CI)	3-year DFS	MST <sup>1</sup> (95% CI)	5-year OS
CRC						
Unilateral disease	NR	59 ± 10%	23 (0-83)	48 ± 10%	NR	73 ± 9%
Bilateral disease	18 (12-24)	26 ± 9%	11 (7-17)	7 ± 5%	51 (24-78)	34 ± 11%
Sarcoma						
Unilateral disease	NR	60 ± 13%	15 (7-24)	14 ± 9%	48 (38-58)	35 ± 15%
Bilateral disease	NR	60 ± 10%	10 (6-14)	35 ± 9%	38 (25-51)	32 ± 9%

<sup>1</sup> Time in months

TTLPP: time to local pulmonary progression; PPFS: pulmonary progression free survival; TTP: time to progression; DFS: disease free survival; MST: median survival time; OS: overall survival; HVC: high volume centre; LVC: Low volume centre; CRC: colorectal carcinoma

### Literature:

- CRC
  - TTLPP: 12-19 mos
  - 3-year PPFS:
    - Unilateral: 55%
    - Bilateral: 12%
  - TTP: 12-52 mos
  - 3-year DFS: 44%
    - 1 study
    - 26% bilateral procedures
  - MST: 31-75 mos
  - 5-year OS: 34-68
- Sarcoma
  - TTLPP: 13-18 mos
  - 3-year PPFS: 44-45%
  - TTP: 7-8 mos
  - 3-year DFS: 25-26%
  - MST: 19-48 mos
  - 5-year OS: 22-53%



# Phase II trial

## Conclusions

- isolated lung perfusion with melphalan combined with metastasectomy is feasible and safe
  - no perioperative † - postoperative complications  $\approx$  regular thoracic procedures
  - no long-term pulmonary toxicity





# Phase II trial

## Conclusions

- compared to historical controls, ILuP with melphalan combined with pulmonary metastasectomy seems beneficial in pts with PM from CRC and sarcoma tumours
  - ILuP shows better local control compared to retrospective literature data, especially in unilateral disease
  - for sarcoma patients this local control markedly diminished general disease progression





# Phase II trial

## Conclusions

- treatment of undetected micrometastases is needed
- further evaluation of locoregional lung perfusion techniques with other chemotherapeutic drugs, a RCT and with adjuvant intravenous therapy is warranted

