

# Identification of prognostic biomarkers in patients undergoing pulmonary metastasectomy from primary colorectal cancer

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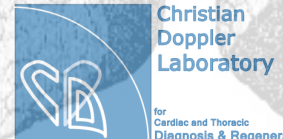


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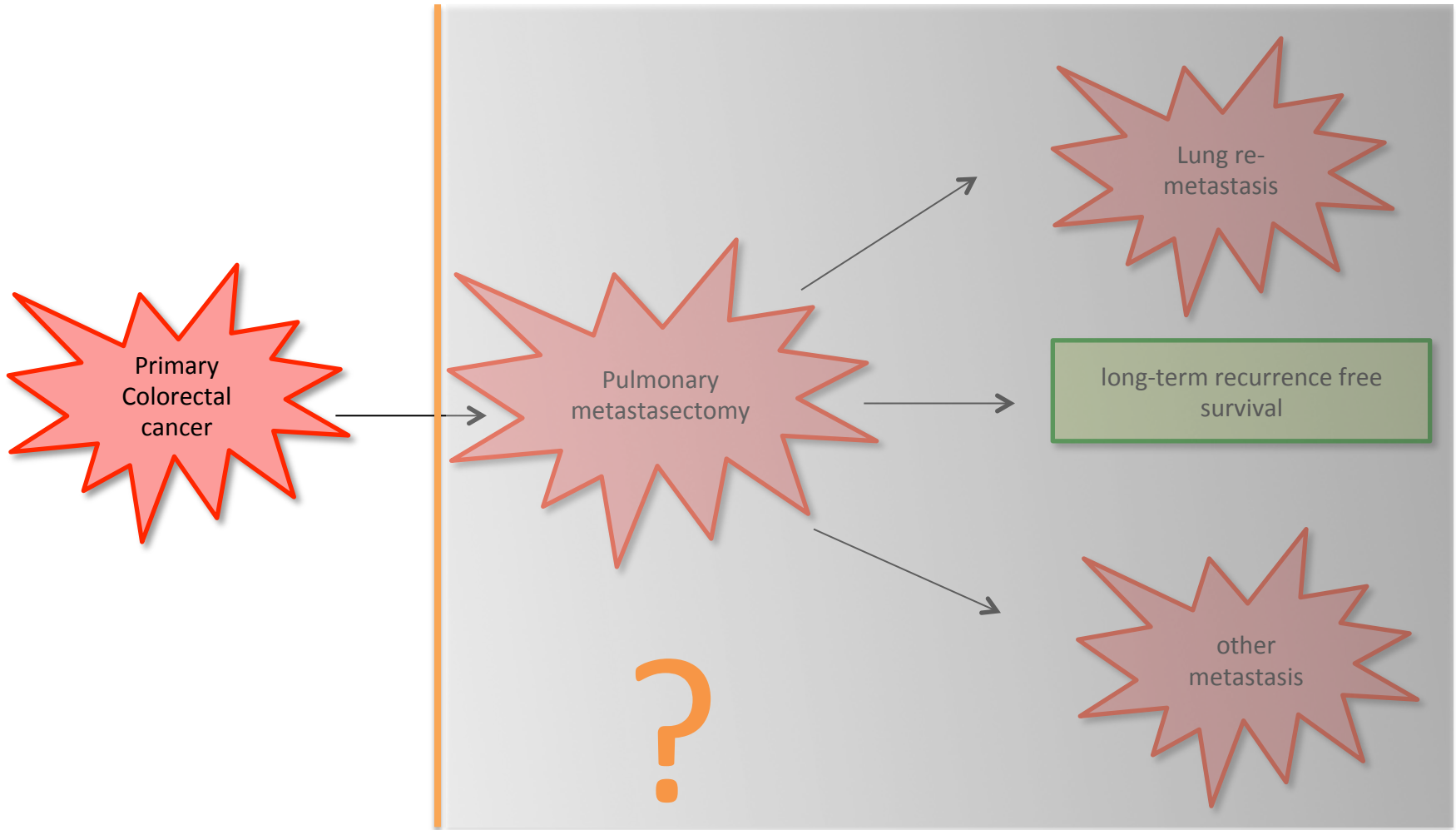
## II. Results and Conclusion

- i. EGFR, BRAF and KRAS status in patients undergoing pulmonary metastasectomy from primary colorectal carcinoma: a prospective follow-up study
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# Introduction

## Prognostic factors in pulmonary metastasectomy



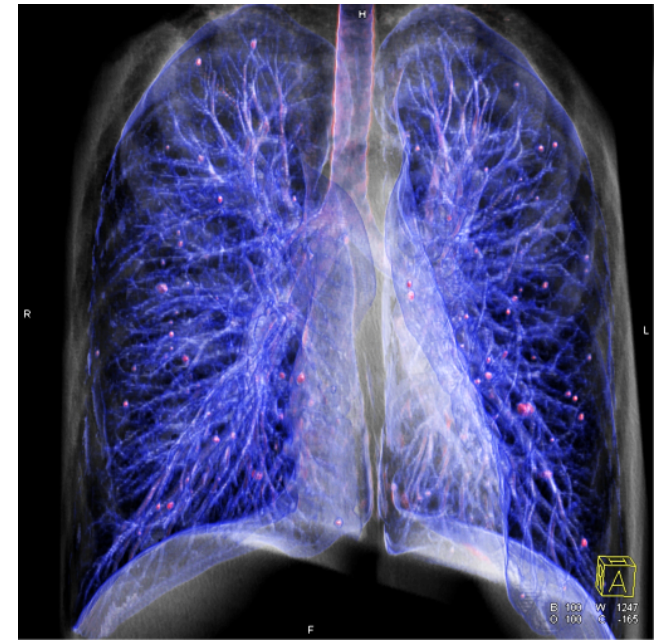
# Introduction

## Prognostic factors in pulmonary metastasectomy

### Clinical Prognostic Factors with impact on overall survival (OS)

Completeness of resection	R1/R2
Number of metastases	> 1 nodule
Disease-free interval (DFI)	< 36 months

International Registry of Lung Metastases, Pastorino et al. 1997

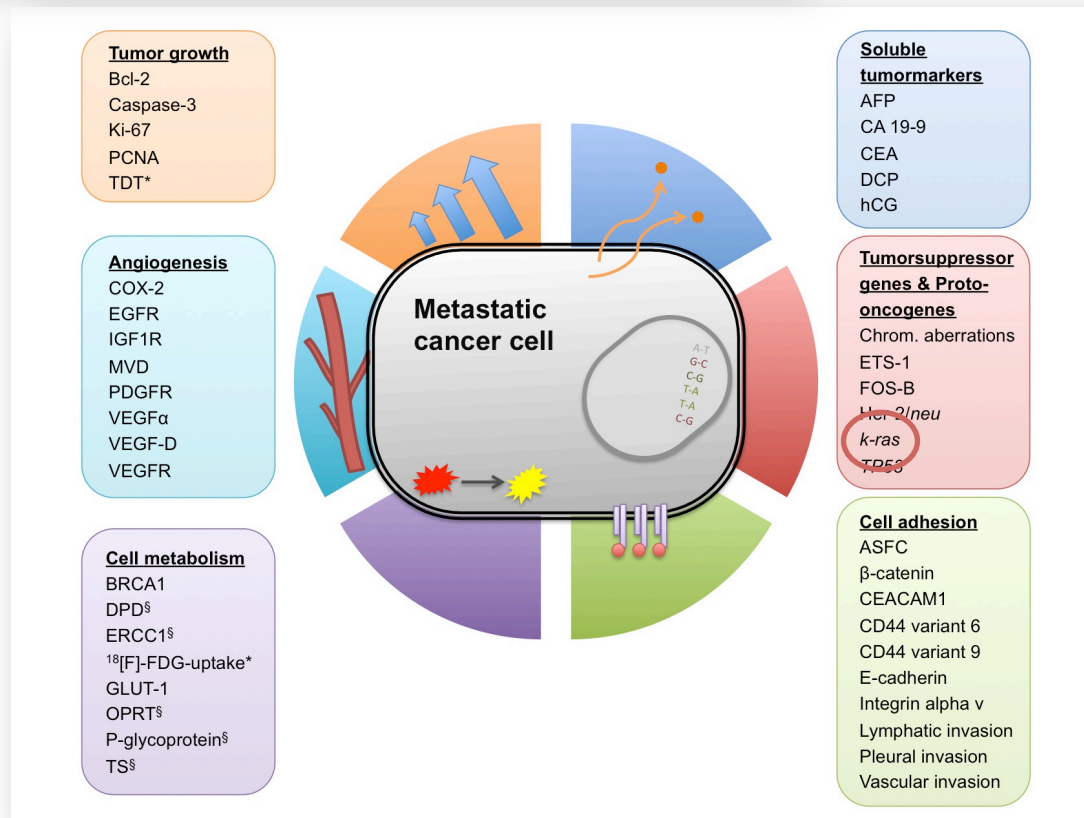


...but so far no **pathohistological factors** reflecting an aggressive tumor biology were established in patients with CRC lung metastases.

# Introduction

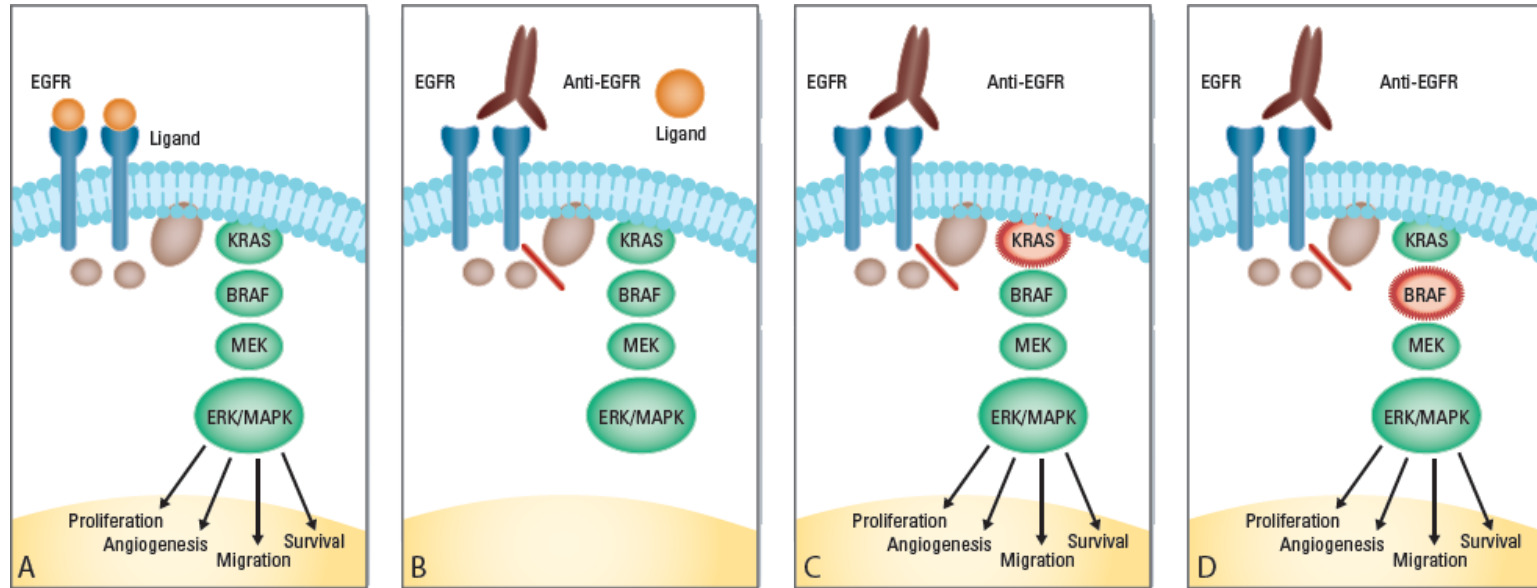
## Prognostic factors in pulmonary metastasectomy: spotlight on molecular and radiological markers

Thomas Schweiger<sup>a,b</sup>, György Lang<sup>a</sup>, Walter Klepetko<sup>a</sup> and Konrad Hoetzenecker<sup>a,b,\*</sup>



# Introduction

## Prognostic factors in pulmonary metastasectomy



Source: GE Healthcare

„...KRAS was mutated significantly more often in primary tumors of patients with lung metastases“  
– Cejas et al. 2009

„...Compared with independent primary cancers, KRAS mutations were more common in lung and brain metastases, but similar in liver metastases“ – Tie et al. 2011

# Results I

Annals of

**SURGICAL ONCOLOGY**

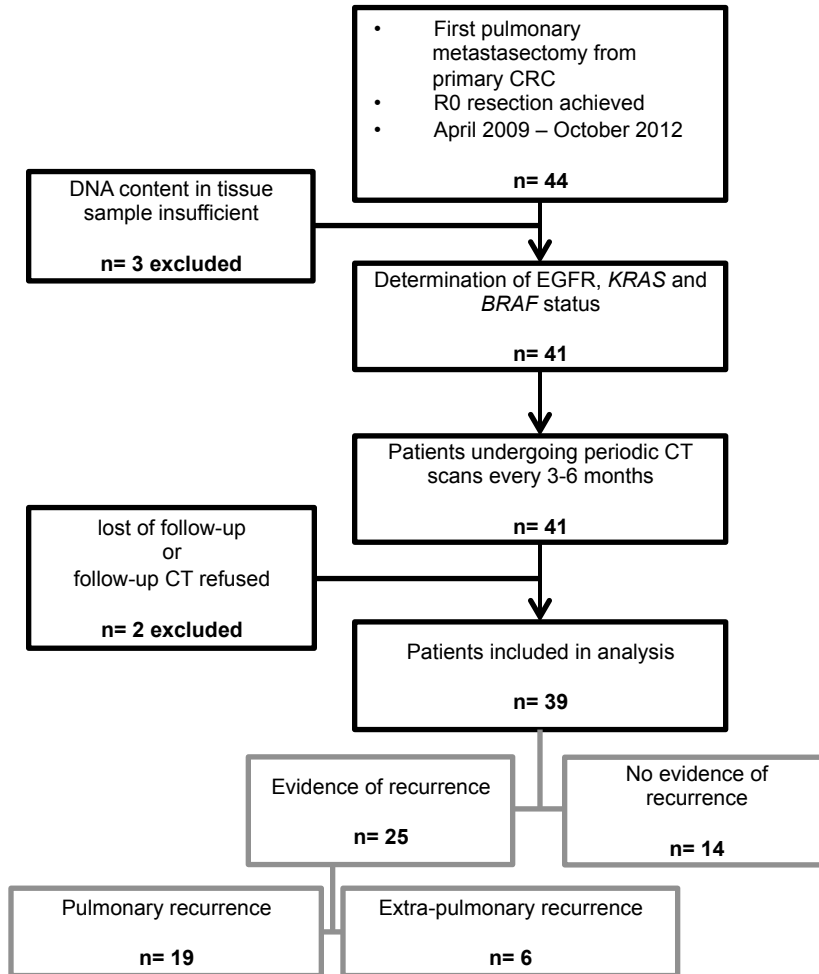
ORIGINAL ARTICLE – THORACIC ONCOLOGY

## **EGFR, *BRAF* and *KRAS* Status in Patients Undergoing Pulmonary Metastasectomy from Primary Colorectal Carcinoma: A Prospective Follow-Up Study**

Thomas Schweiger<sup>1,2</sup>, Balazs Hegedüs, PhD<sup>1</sup>, Christoph Nikolowsky<sup>1,2</sup>, Zita Hegedüs, MSc<sup>3</sup>, Ildiko Szirtes, MD<sup>3</sup>, Roland Mair<sup>1</sup>, Peter Birner, MD<sup>4</sup>, Balazs Döme, MD, PhD<sup>1,5</sup>, György Lang, MD, PhD<sup>1</sup>, Walter Klepetko, MD<sup>1</sup>, Hendrik Jan Ankersmit, MD<sup>1,2</sup>, and Konrad Hoetzenecker, MD, PhD<sup>1</sup>

EGFR, BRAF and KRAS status in patients undergoing pulmonary metastasectomy from primary colorectal carcinoma: a prospective follow-up study. Schweiger T, Hegedüs B, Nikolowsky C, Hegedüs Z, Szirtes I, Mair R, Birner P, Döme B, Lang G, Klepetko W, Ankersmit HJ, Hoetzenecker K. Ann Surg Oncol. 2014 Mar;21(3):946-54. doi: 10.1245/s10434-013-3386-7. Epub 2013 Nov 27.

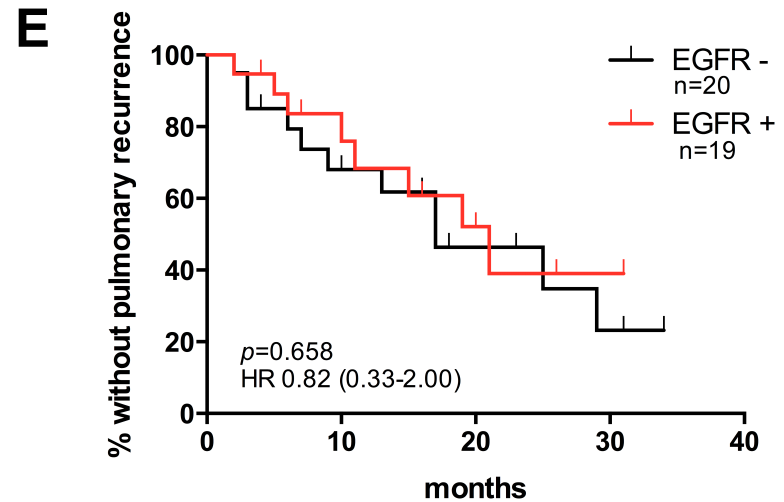
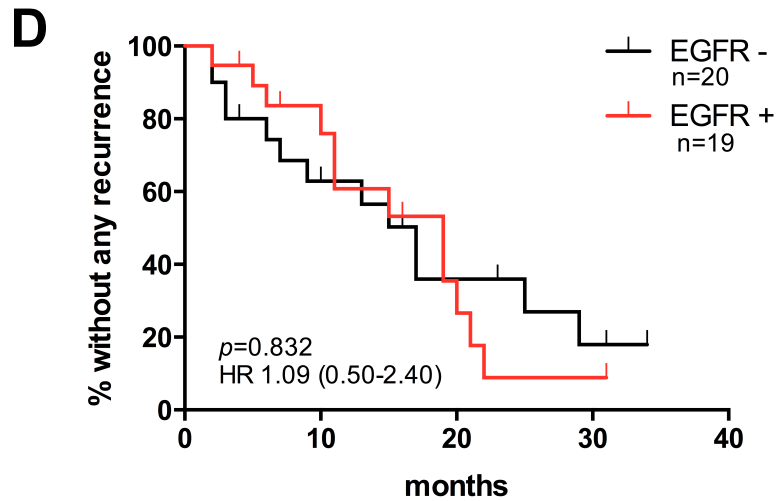
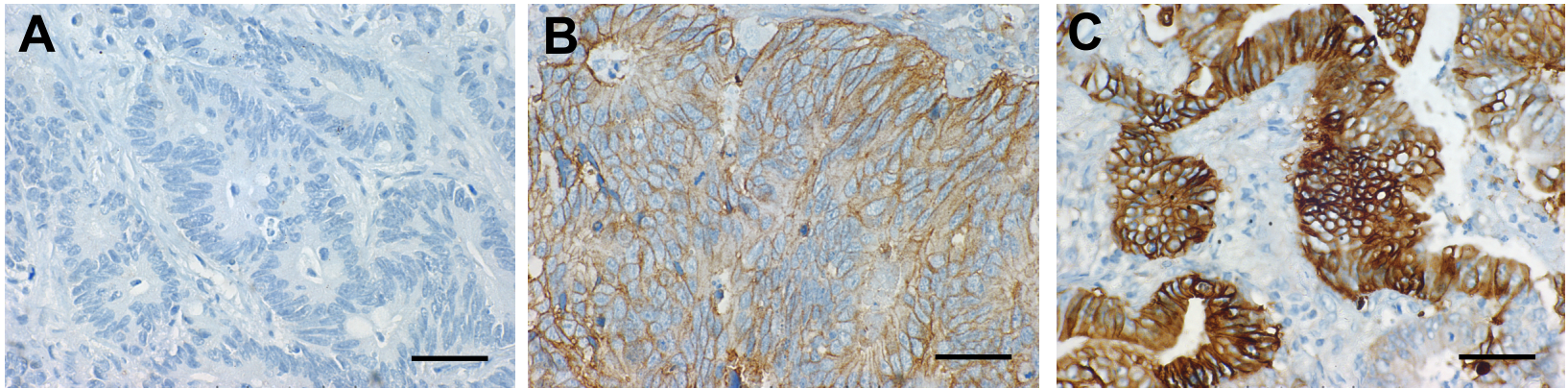
# Results I



Schweiger et al., Ann Surg Oncol (2014)



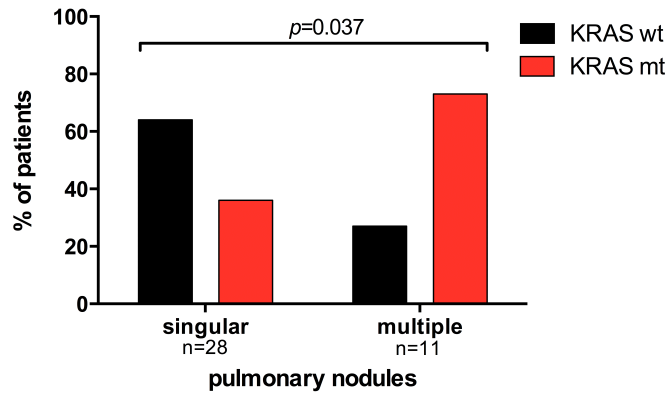
# Results I



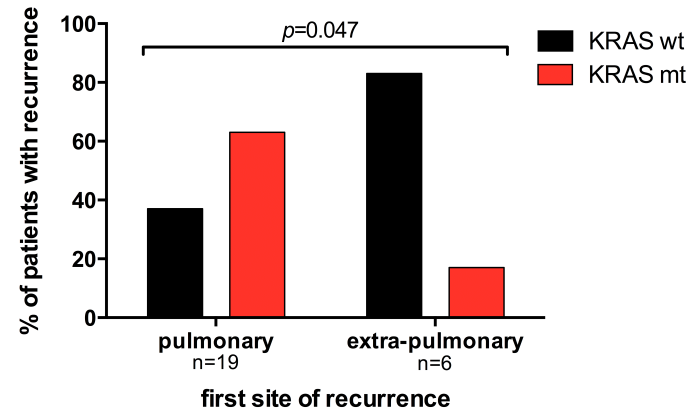
Schweiger et al., Ann Surg Oncol (2014)

# Results I

## A



## B



Schweiger et al., Ann Surg Oncol (2014)

# Conclusions I

- *KRAS* mutations are **evident in a high percentage (53.8%)** of patients with pulmonary metastases
- *KRAS* mutations are associated with **diffuse pulmonary metastasis and early lung-specific recurrence**
- In the future, genotyping of multiple genes might prognosticate the course of metastatic disease

# Conclusions I

## KRAS Mutation Influences Recurrence Patterns in Patients Undergoing Hepatic Resection of Colorectal Metastases

Nancy E. Kemeny, MD<sup>†</sup>, Joanne F. Chou, MPH<sup>\*\*</sup>, Marinela Capanu, PhD<sup>\*\*</sup>, Alexandra N. Gewirtz, BA<sup>†</sup>, Andrea Cercek, MD<sup>†</sup>, T. Peter Kingham, MD<sup>†</sup>, William R. Jarnagin, MD<sup>†</sup>, Y Fong<sup>†</sup>, Ronald P. DeMatteo, MD<sup>†</sup>, Peter J. Allen<sup>†</sup>, Jinru Shia, MD<sup>‡</sup>, Celina Ang, MD<sup>†</sup>, Efsevia Vakiani, MD<sup>‡</sup>, and Michael I. D'Angelica, MD<sup>†</sup>

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# BJC

British Journal of Cancer (2015) 112, 424–428 | doi: 10.1038/bjc.2014.619

Keywords: colorectal cancer; lung metastases; KRAS; overall survival

## Association between KRAS mutation and lung metastasis in advanced colorectal cancer

A A L Pereira<sup>\*1</sup>, J F M Rego<sup>1</sup>, V Morris<sup>2</sup>, M J Overman<sup>3</sup>, C Eng<sup>3</sup>, C R Garrett<sup>3</sup>, A T Boutin<sup>4</sup>, R Ferrarotto<sup>5</sup>, M Lee<sup>2</sup>, Z-Q Jiang<sup>3</sup>, P M Hoff<sup>1</sup>, J-N Vauthey<sup>6</sup>, E Vilar<sup>7</sup>, D Maru<sup>8</sup> and S Kopetz<sup>3</sup>

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....cited 15 times according Scopus (June 2016)

# Interlude

## Heat-shock protein 27 and activated fibroblasts

# Interlude Hsp27 & Fibroblasts

## Discrimination of clinical stages in non-small cell lung cancer patients by serum HSP27 and HSP70: A multi-institutional case-control study

Matthias Zimmermann <sup>a,1</sup>, Stefanie Nickl <sup>a,1</sup>, Christopher Lambers <sup>b</sup>, Stefan Hacker <sup>a</sup>, Andreas Mitterbauer <sup>a</sup>, Konrad Hoetzenecker <sup>a,c</sup>, Anita Rozsas <sup>d</sup>, Gyula Ostoros <sup>d</sup>, Viktoria Laszlo <sup>c</sup>, Helmut Hofbauer <sup>a</sup>, Ferenc Renyi-Vamos <sup>c,e</sup>, Walter Klepetko <sup>c</sup>, Balazs Dome <sup>c,d</sup>, Hendrik Jan Ankersmit <sup>a,c,\*</sup>

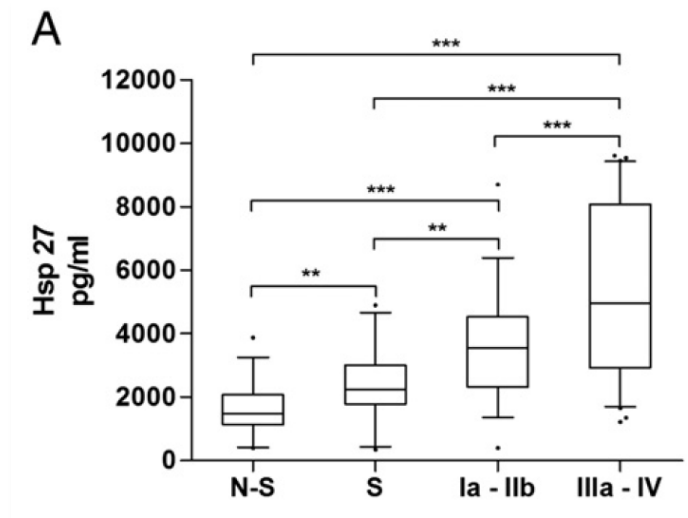
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# Results II

RESEARCH ARTICLE

## Stromal Expression of Heat-Shock Protein 27 Is Associated with Worse Clinical Outcome in Patients with Colorectal Cancer Lung Metastases

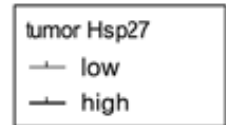
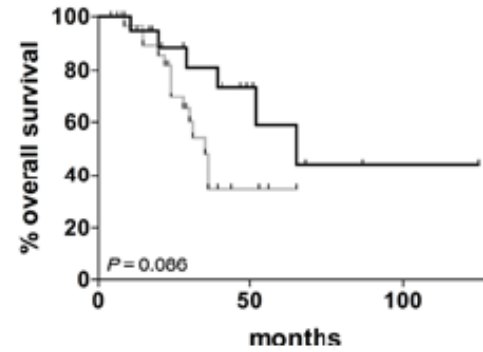
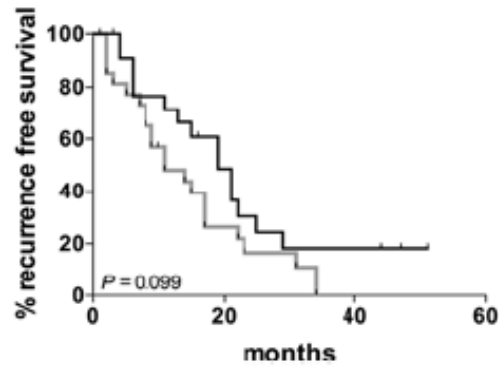
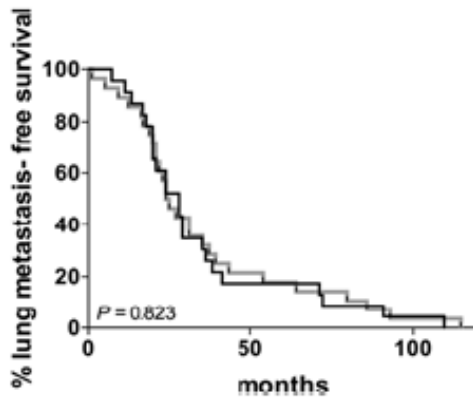
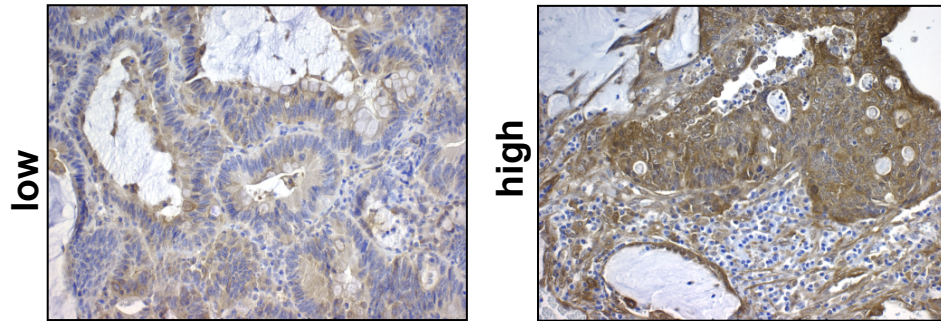
Thomas Schweiger<sup>1,2</sup>, Christoph Nikolowsky<sup>1,2</sup>, Patrick Starlinger<sup>3</sup>, Denise Traxler<sup>1,2</sup>, Matthias Zimmermann<sup>2</sup>, Peter Birner<sup>4,7</sup>, Balazs Hegedüs<sup>1,5,6,7,10</sup>, Balazs Dome<sup>1,7,8,9,10</sup>, Michael Bergmann<sup>3</sup>, Michael Mildner<sup>11</sup>, Walter Klepetko<sup>1</sup>, Konrad Hoetzenecker<sup>1,2</sup>, Hendrik Jan Ankersmit<sup>1,2\*</sup>



# Results II

## Tumor cells

Hsp 27





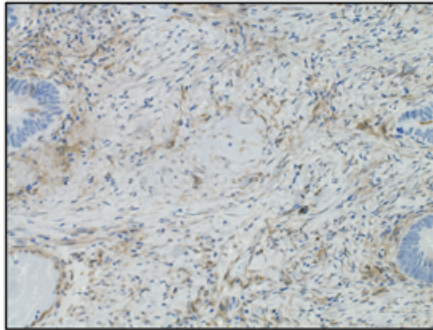
# Results II

## Tumor stroma

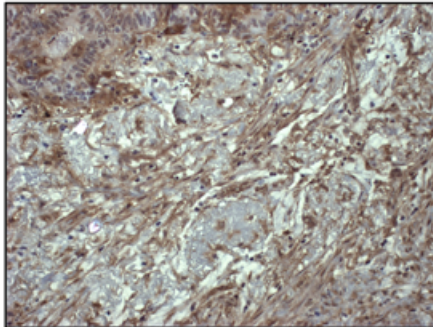
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Hsp27

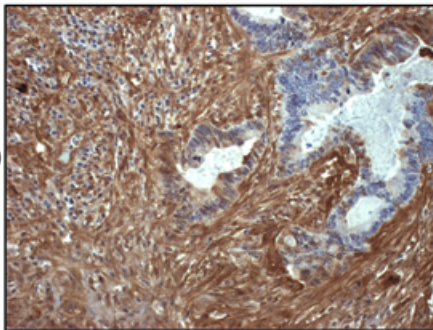
low



intermediate

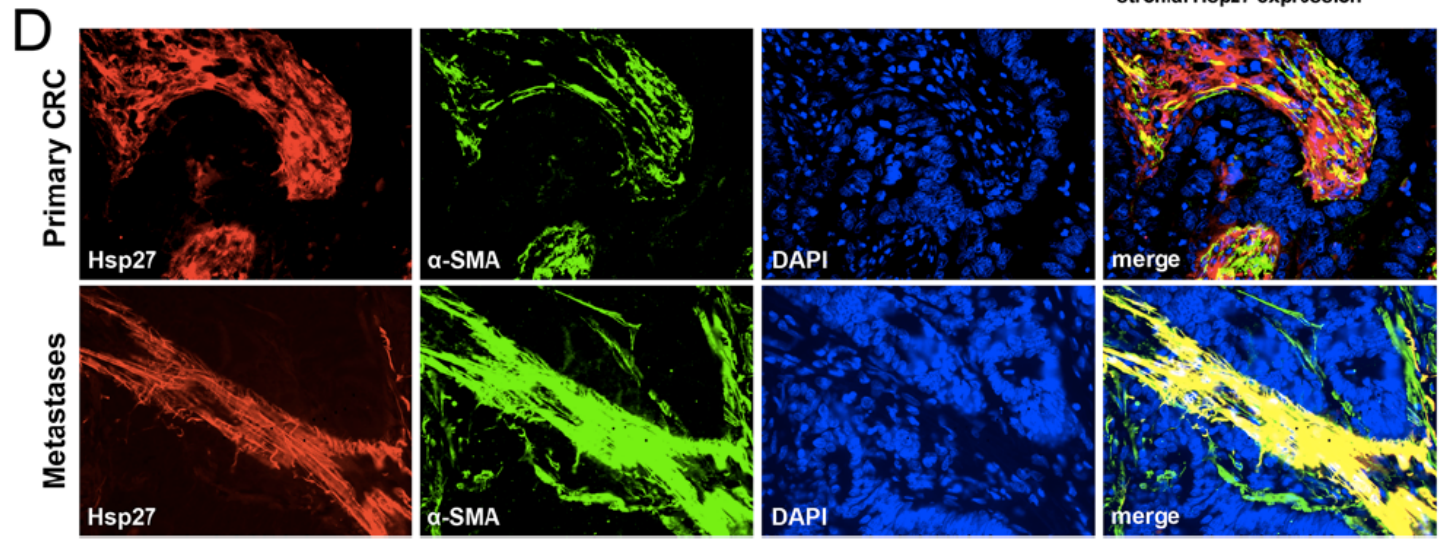
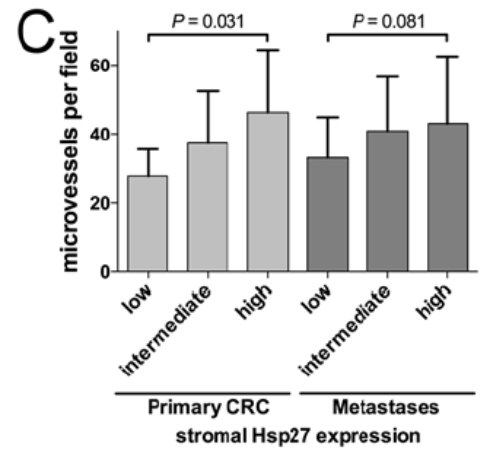
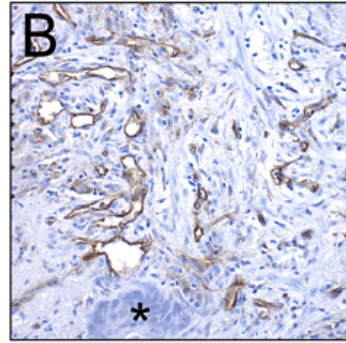
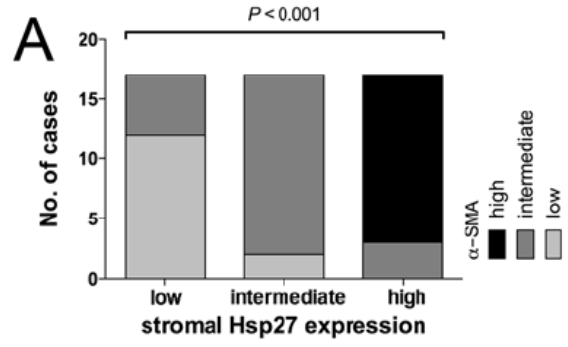


high



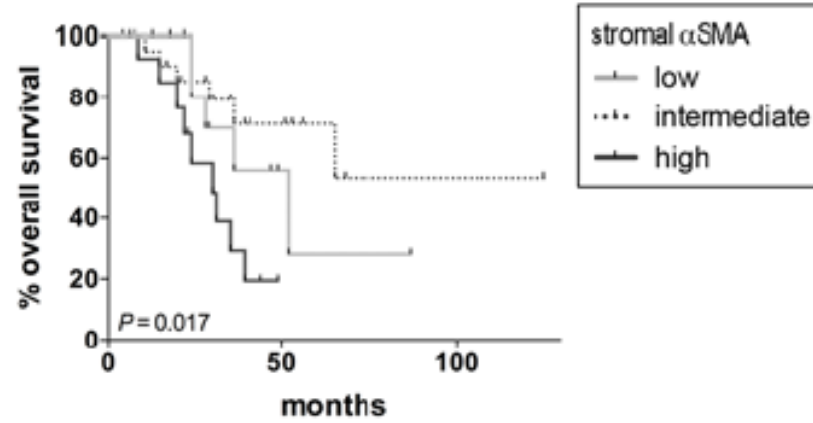
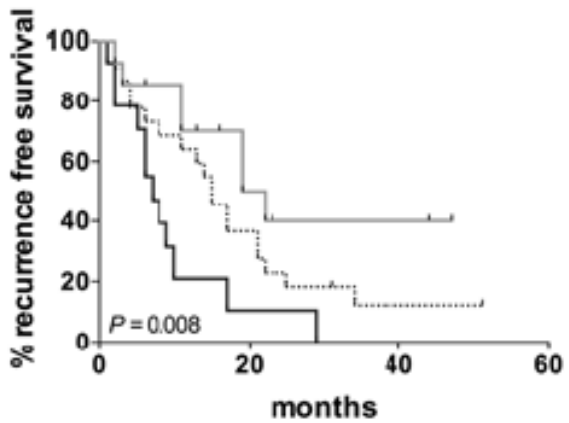
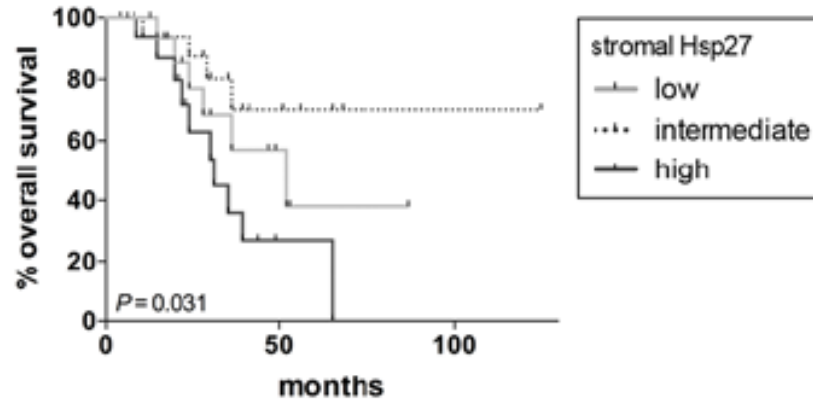
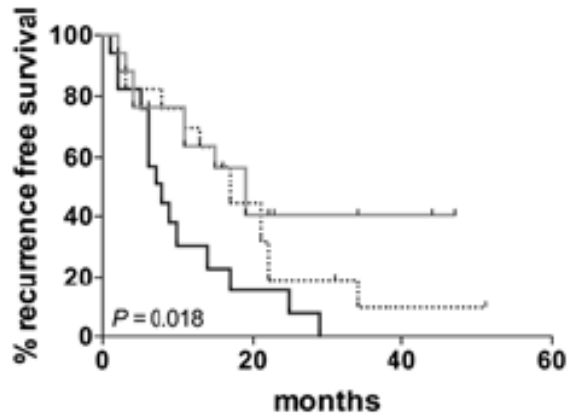
Schweiger et al., PLOS One (2015)

# Results II



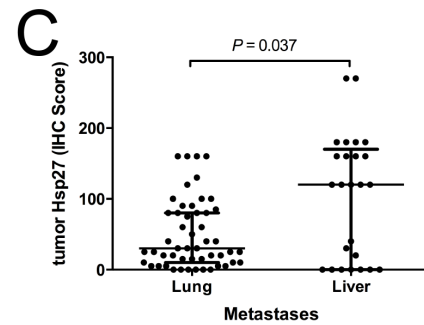
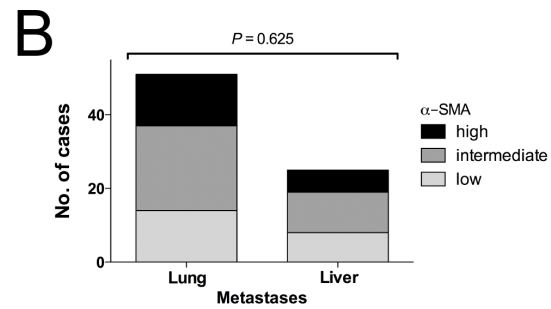
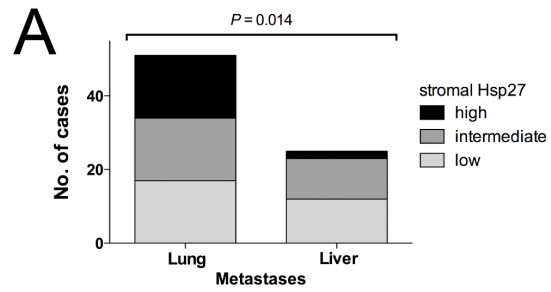
Schweiger et al., PLOS One (2015)

# Results II



Schweiger et al., PLOS One (2015)

# Results II



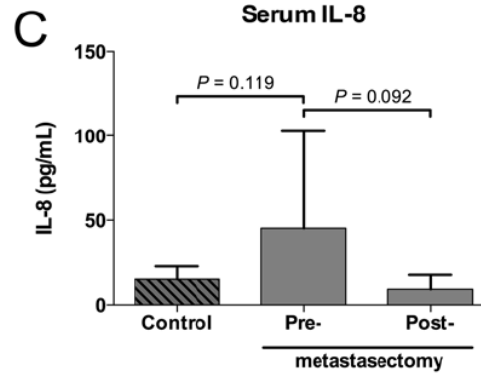
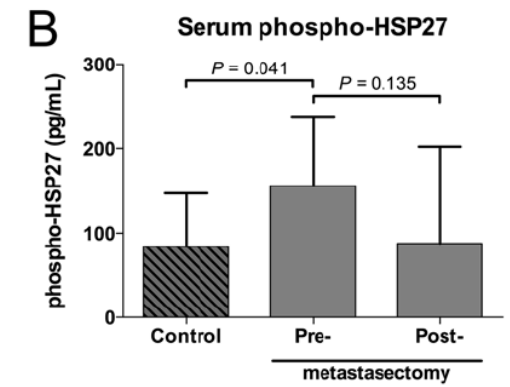
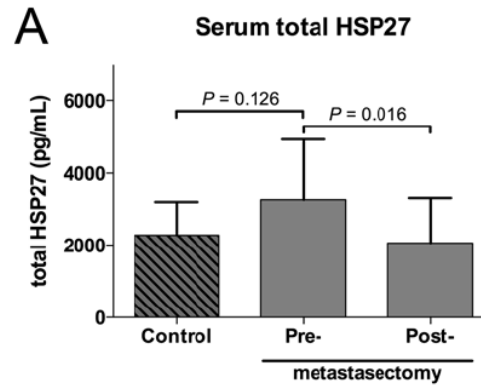
# Results II

pre-operative



Source: greiner bio-one

3 months post-operative

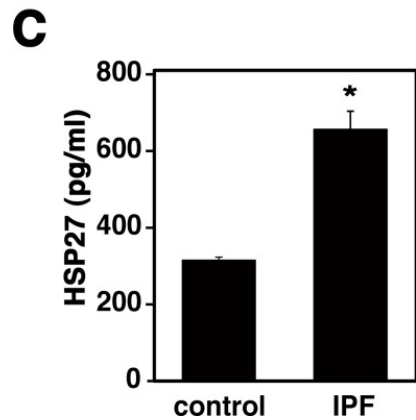
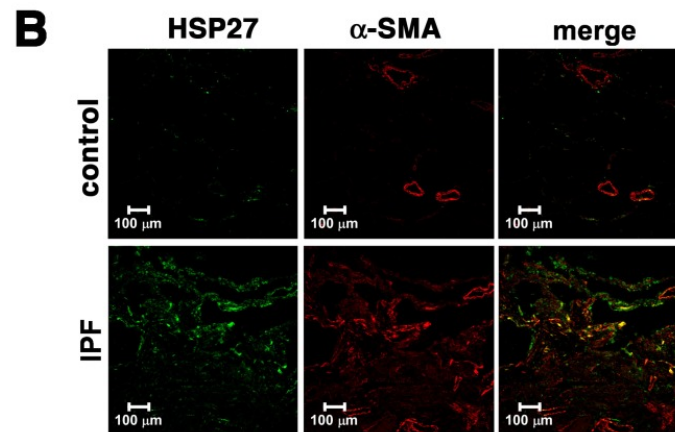
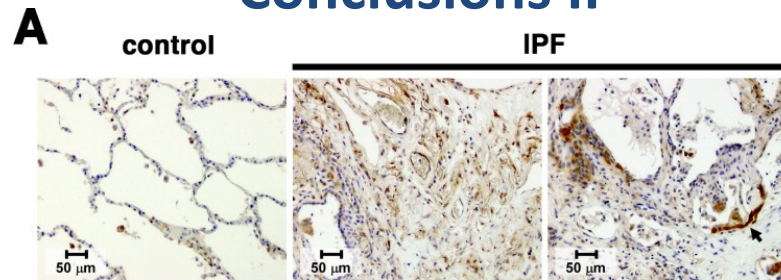


Schweiger et al., PLOS One (2015)

## Conclusions II

- Hsp27 is **highly expressed in tumor-associated fibroblasts** and correlates with the expression of alpha-smooth muscle actin
- Pulmonary metastases with highly Hsp27<sup>+</sup> tumor-associated fibroblasts exhibit **increased neoangiogenesis**
- Hsp27<sup>+</sup>/alpha-SMA<sup>+</sup> fibroblasts are associated **with decreased recurrence-free survival/overall survival** after pulmonary metastasectomy
- Total- and phospho-Hsp27 is **systemically increased before pulmonary metastasectomy** and decreases after surgery

# Conclusions II



PLoS One. 2016 Feb 9;11(2):e0148998.  
Heat Shock Protein 27 Plays a Pivotal Role in Myofibroblast Differentiation and  
in the Development of Bleomycin-Induced Pulmonary Fibrosis.

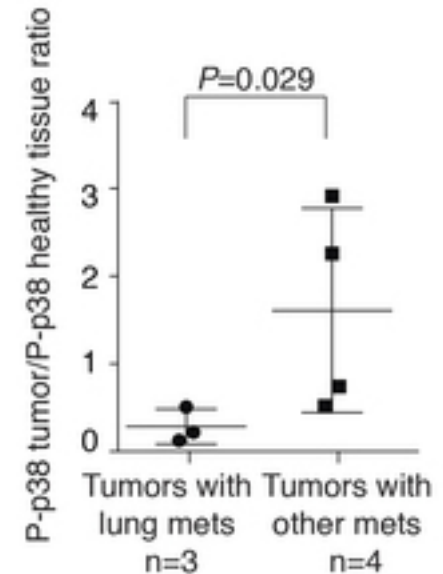
# Conclusions II

nature  
cell biology

Colon cancer cells colonize the lung from established liver metastases through p38 MAPK signalling and PTHLH

Jelena Urosevic<sup>1,8</sup>, Xavier Garcia-Albéniz<sup>1,2,8</sup>, Evarist Planet<sup>1</sup>, Sebastián Real<sup>1</sup>, María Virtudes Céspedes<sup>3,4</sup>, Marc Guiu<sup>1</sup>, Esther Fernandez<sup>1</sup>, Anna Bellmunt<sup>1</sup>, Sylwia Gawrzak<sup>1</sup>, Milica Pavlovic<sup>1</sup>, Ramon Mangués<sup>3,4</sup>, Ignacio Dolado<sup>1,7</sup>, Francisco M. Barriga<sup>1</sup>, Cristina Nadal<sup>2</sup>, Nancy Kemeny<sup>5</sup>, Eduard Batlle<sup>1,6</sup>, Angel R. Nebreda<sup>1,6</sup> and Roger R. Gomis<sup>1,6,9</sup>

„...reduced p38 MAPK signalling endows cancer cells with the ability to form lung metastasis...“





# Limitations

- limited number of patients
- highly selected study cohort
- heterogeneity regarding chemotherapeutic pre-treatment
- methodical limitations, e.g. no automated image analysis, FFPE samples

## **Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis and Regeneration**

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## **Surgical Research Facility**

Michael Bergmann

Patrick Starlinger

## **Clinical Institute of Pathology**

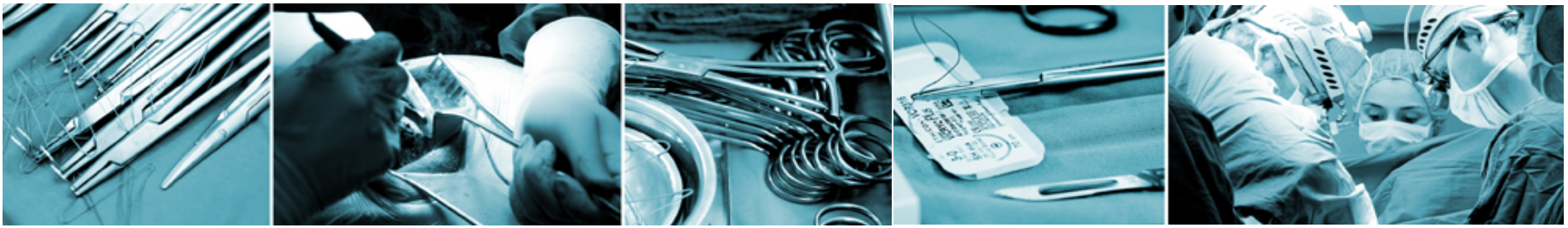
Peter Birner

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# Identification of prognostic biomarkers in patients undergoing pulmonary metastasectomy from primary colorectal cancer

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