SURGERY OF OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER

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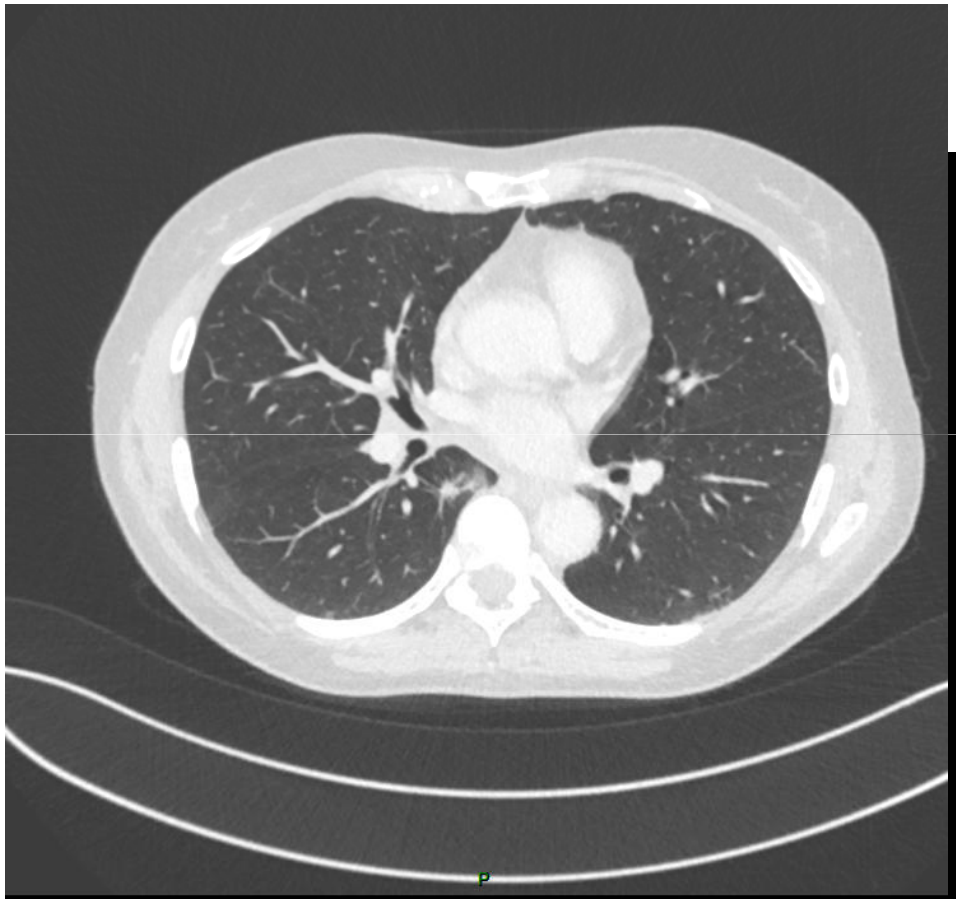
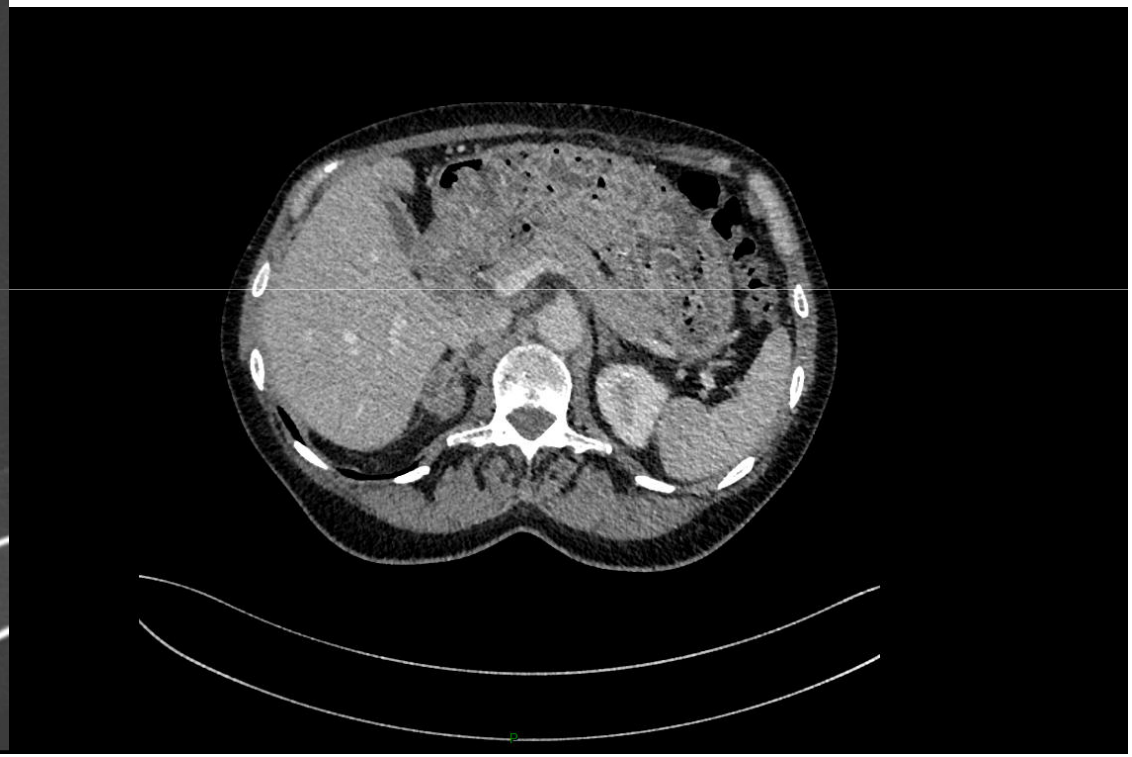
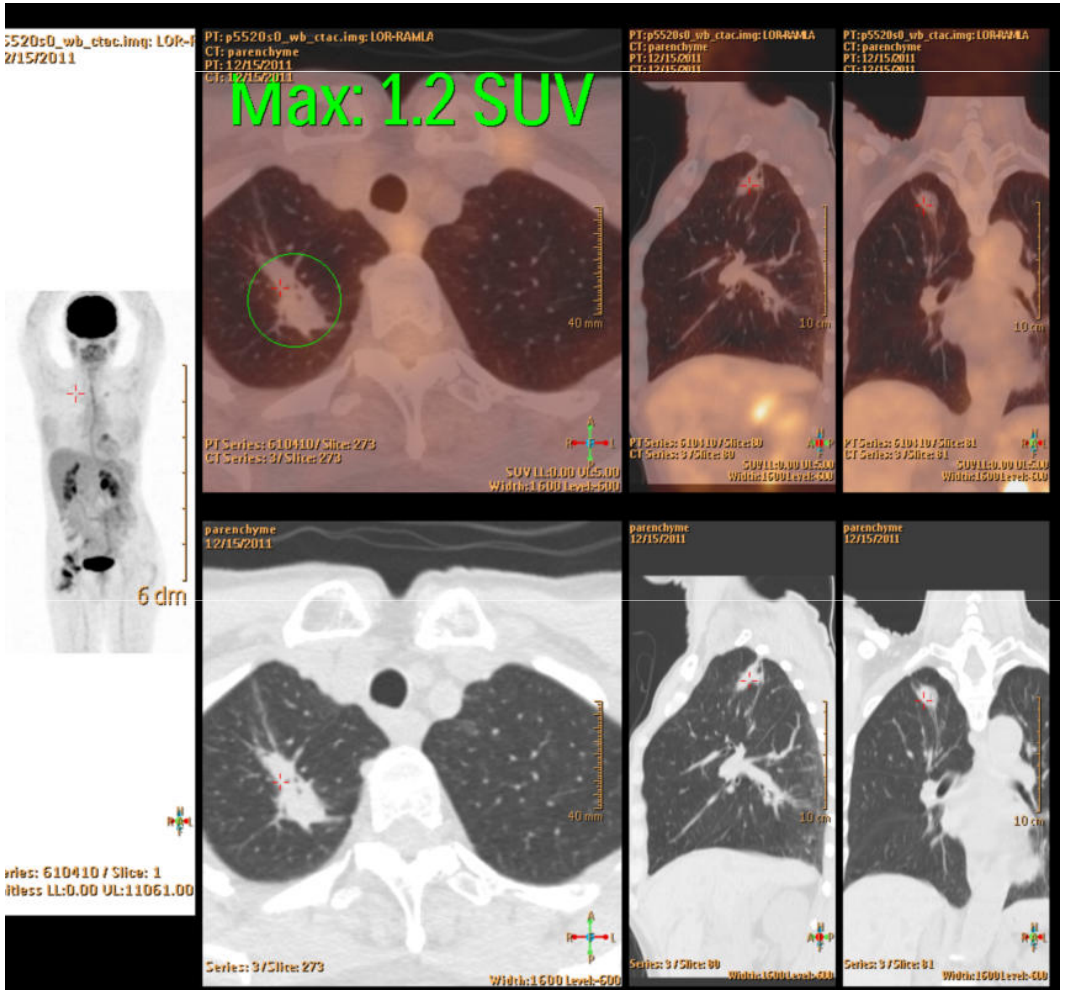
W, 51 years
ADK cT1N1M+ RLL
Chemotherapy (Cys-Platin Pemetrexed), 4 cycles
Right lower lobectomy and right adrenalectomy through phrenotomy
Uneventful postoperative course

No disease relapse at 23 months



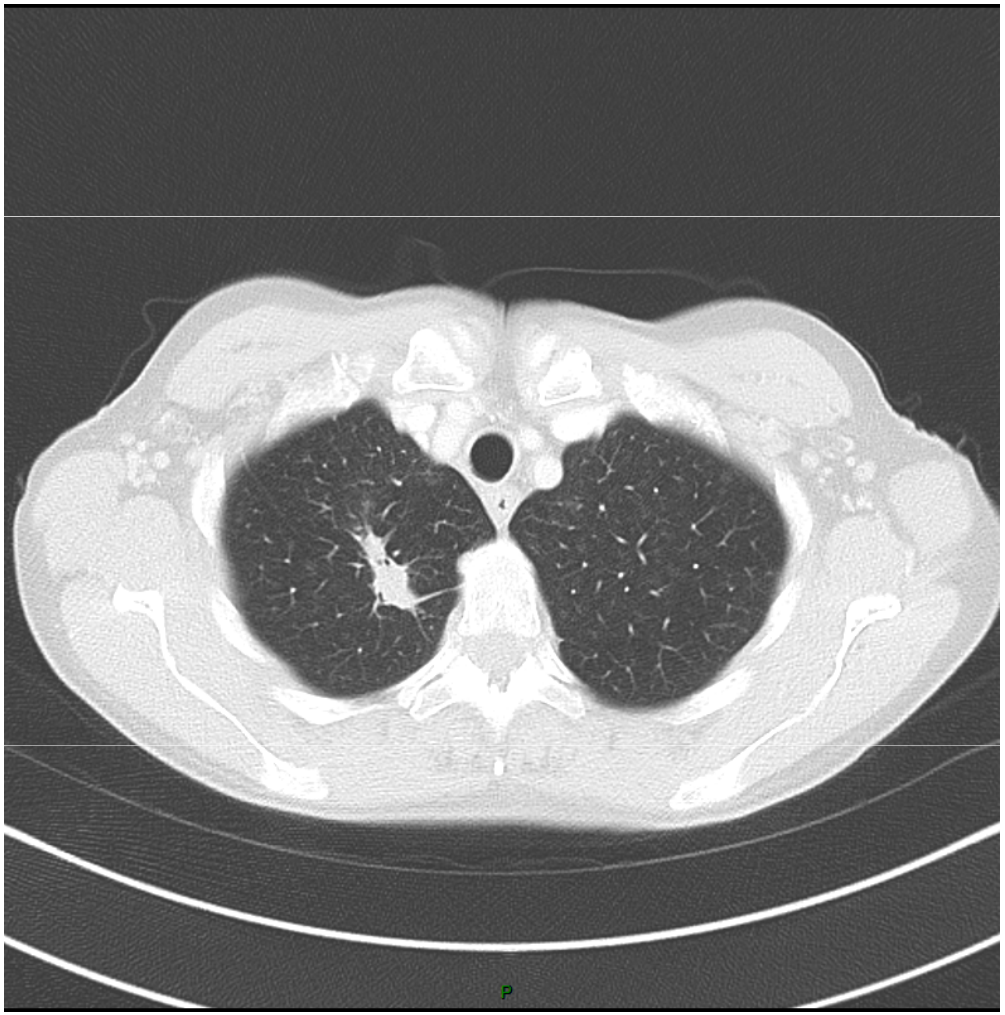


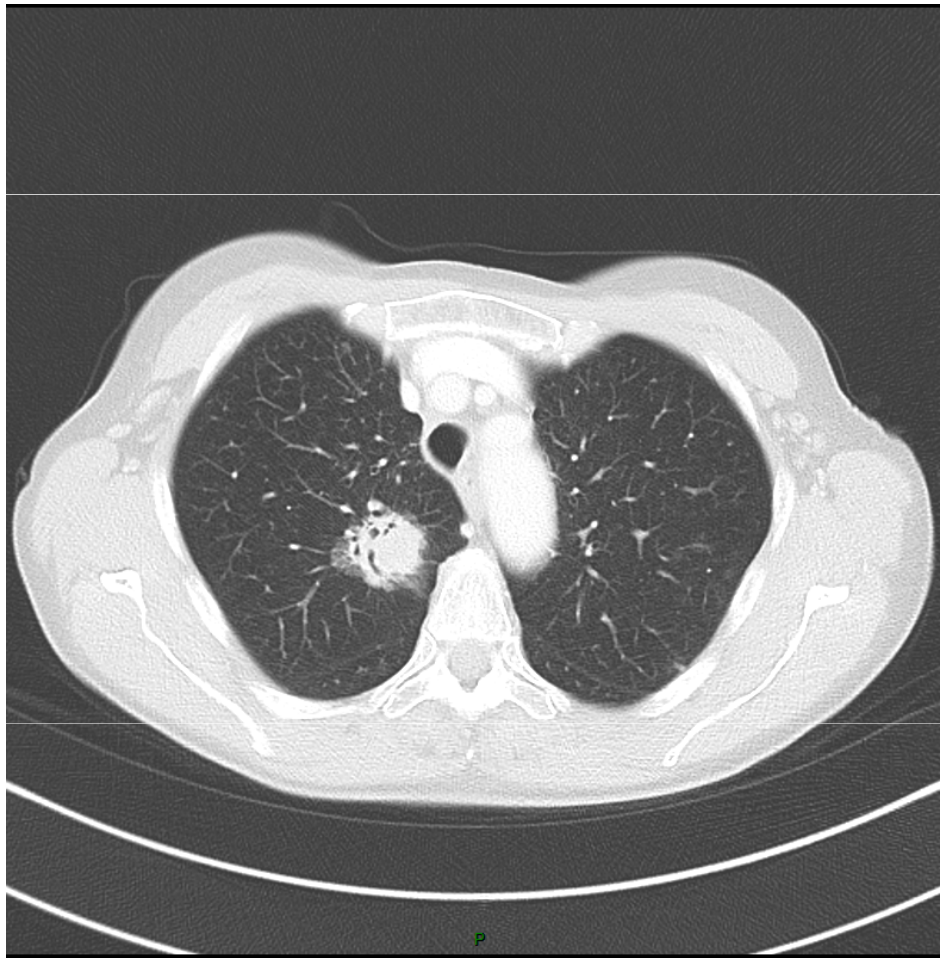
W, 64 years
ADK cT2N2M+ RUL
Chemotherapy (Cys-Platin Pemetrexed Bevacizumab), 6 cycles, then Pemetrexed Bevacizumab (6 cycles)
RUL: PR; SUV max 1,2, stable over 6 months; no nodal uptake; right adrenal gland SUV 7,5



March 2013
Right adrenalectomy; uneventful postoperative course
Pathology: Adenocarcinoma; 70% necrosis

Avril 2014

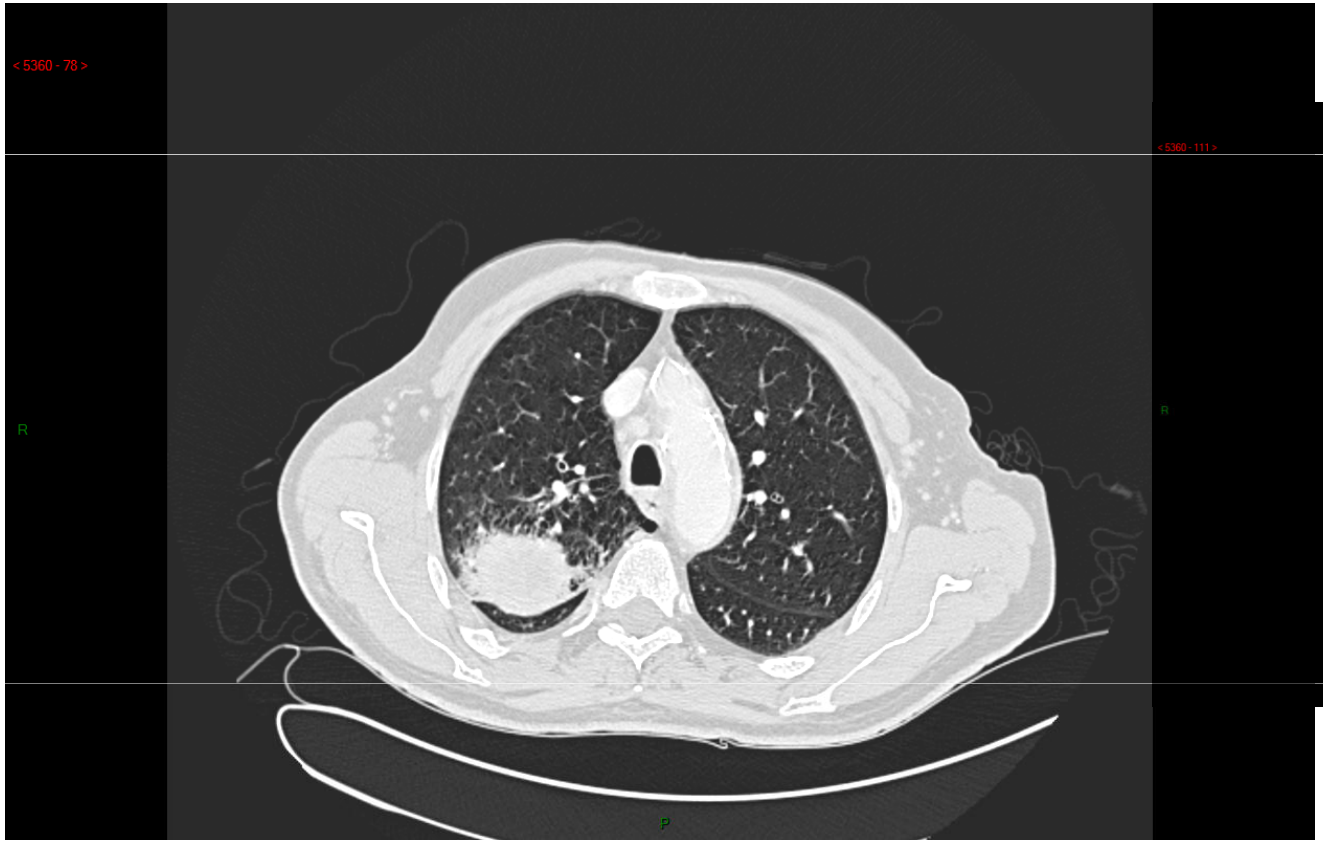


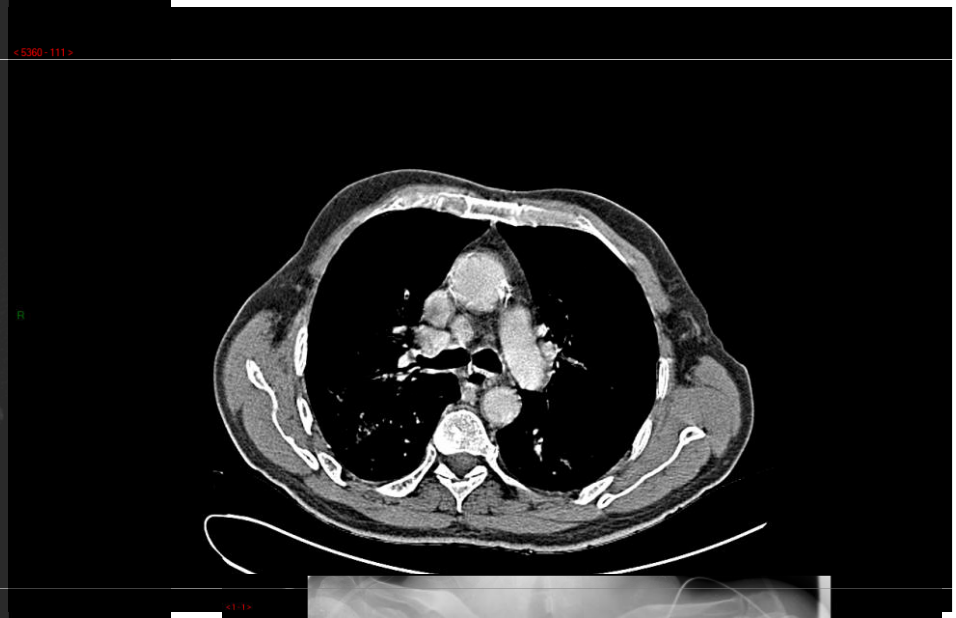


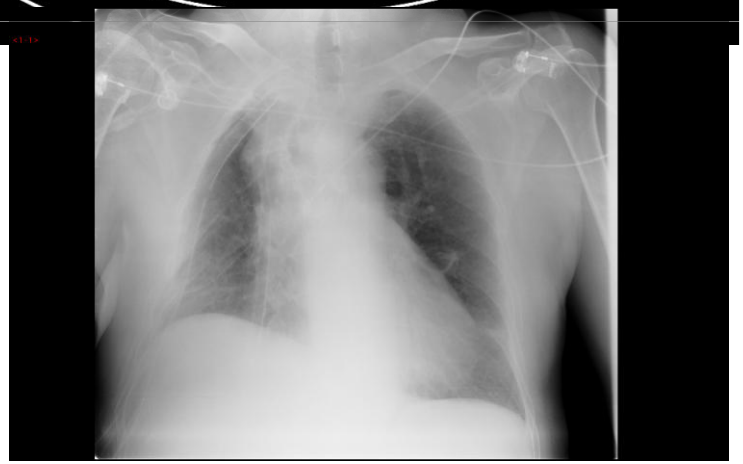
RU lobectomy, nodal dissection
pT2N0;
Alive and disease-free at 3 years

M, 68 years
ADK (tubular) cT2N2M0 RUL
Chemotherapy (Cys-Platin Pemetrexed), 3 cycles: PR,

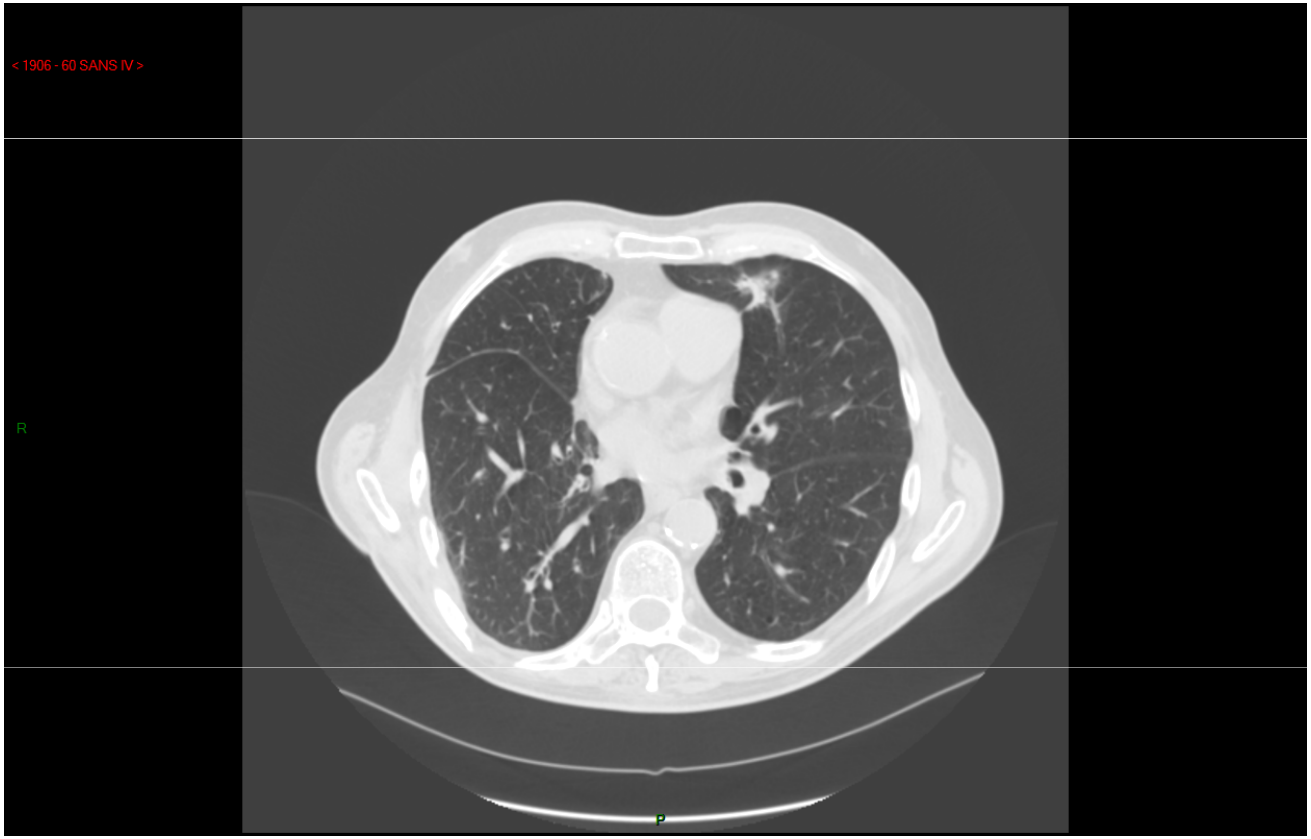
August 2009: sleeve RUL: ypT2N1M0



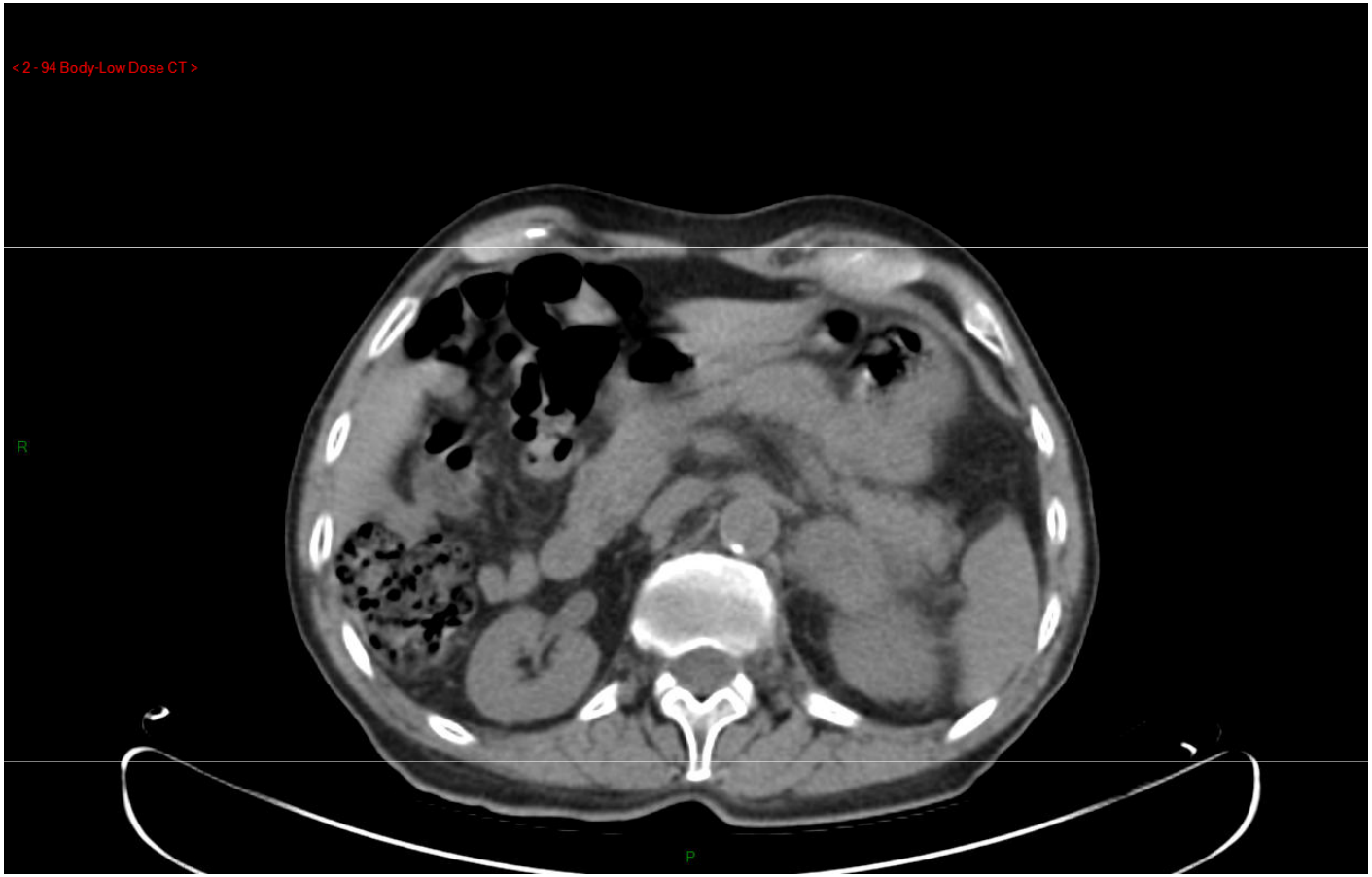




2011 lingular relapse: resection of lingula + Thyroidectomy (nodule)
ADK (tubular) pT1N0; thyroid metastasis
Postoperative chemotherapy: Carboplatin Pemetrexed (6 cycles)



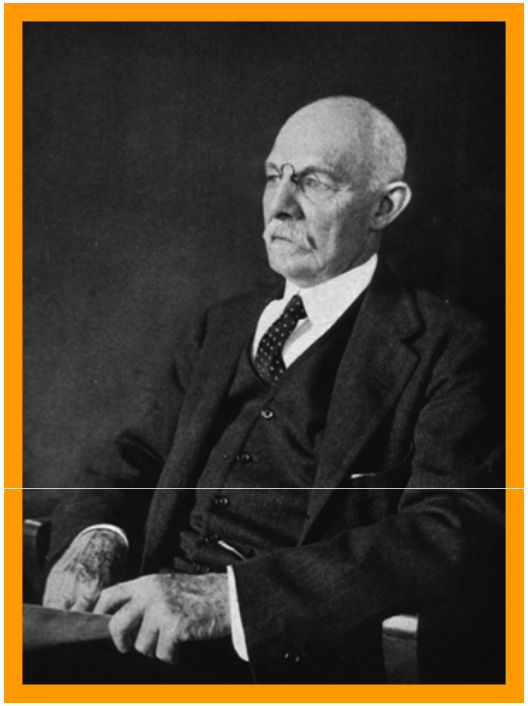
2013 left adrenal metastasis: adrenalectomy
ADK (tubular) R0
Postoperative chemotherapy: Pemetrexed Bevacizumab (6 cycles)



2015: PD: no local relapse; brain and bone metastasis; fatal outcome

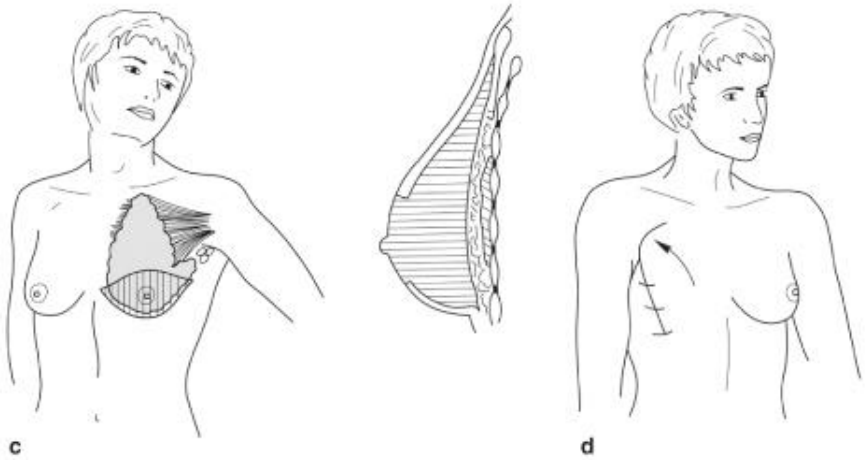
The principles of modern surgical therapy of cancer have seen established by Sir

William Stewart Halsted (1852 – 1922)



CANCER IS A DISEASE WICH SPREAD "ORDERLY"
FIRST LOCALLY,
THAN REGIONALY
AND LATELY SYSTEMIC.

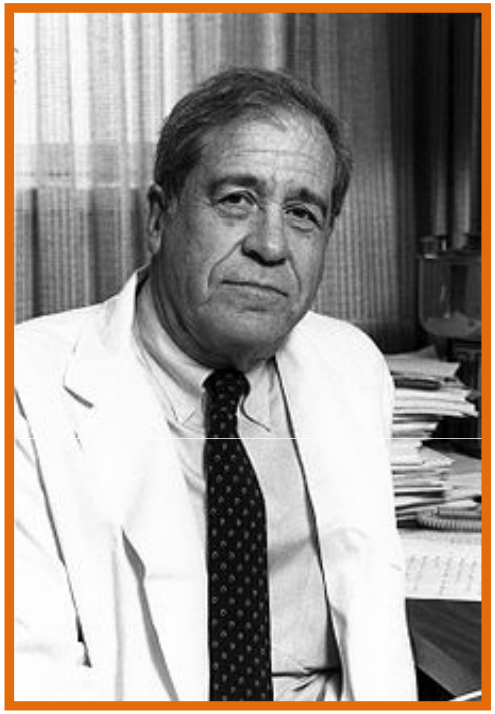
A RADICAL LOCAL CONTROL LEADS TO A DEFINITIVE CURE OF THE DISEASE.



Radical Mastectomy

The theory of the “orderly” spread of cancer was contradicted by the work of surgeon

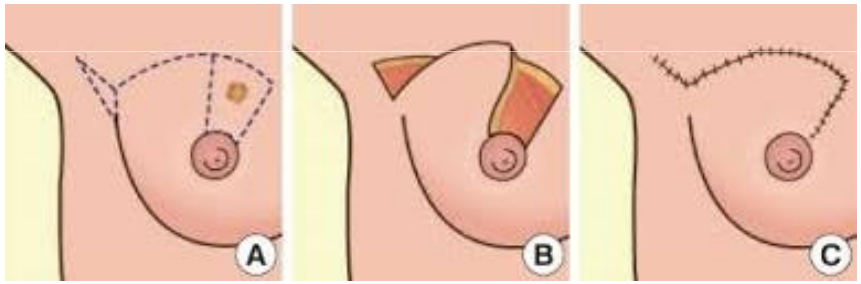
Bernard Fischer (1918-)



demonstration of the presence of “Tumoral circulant cells” in the early stage of the disease.

CANCER IS A SYSTEMIC DISEASE SINCE ITS EARLY PHASE

A less extensive surgery leads to the same control of the disease.



lumpectomy

In 1995 a new state of cancer termed "**OLIGOMETASTASES**" has been theorized by *S. Hellman and RR Weichselbaum* to describe an **intermediate state** between localized and systemic disease.

OLIGOMETASTSES is a state of cancer defined as the presence of limited systemic disease.

Where "**Limited**" could be defined as to one or a fixed number of metastases, for whom the use of a local treatment modality could achieve a disease free status.

- None of these theories is comprehensive of the whole panel of phenomenon of cancer development and diffusion.

- The theories of **XX$_{th}$ century** has been dominated by an **«ANATOMO-CLINICAL»** vision of cancer.

- The **XXI$_{th}$ century** is characterized by **«BIOLOGICAL»** demonstration of cancer rules of development and diffusion.

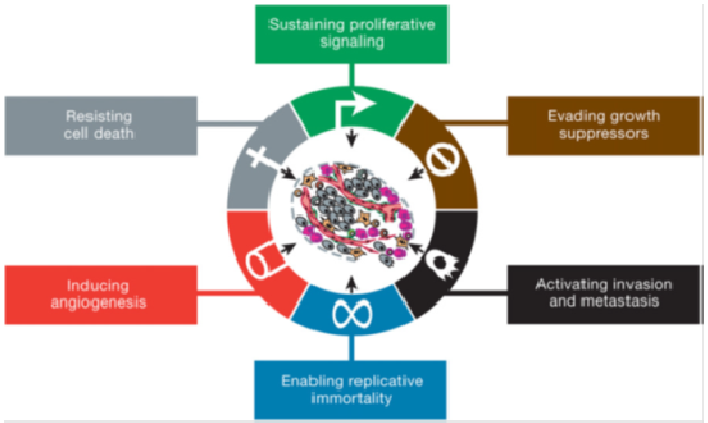
Biology before Anatomy in Early Breast Cancer — Precisely the Point
Clifford A. Hudis, M.D.
N Engl J Med 2015; 373:2079-2080

The "**Hallmarks of Cancer**"

Hanahan D and Weinberg RA in 2000

"Tumors are more than insular masses of proliferating cancer cells"

"They are complex tissues composed of multiple distinct cell types that participate in heterotypic interactions with one another"



In 2000 from a biological point of view the determinants of cancer were almost exclusive intrinsic to cancer cells.

Hallmarks of Cancer: The Next Generation

Hanahan D and Weinberg RA in 2011

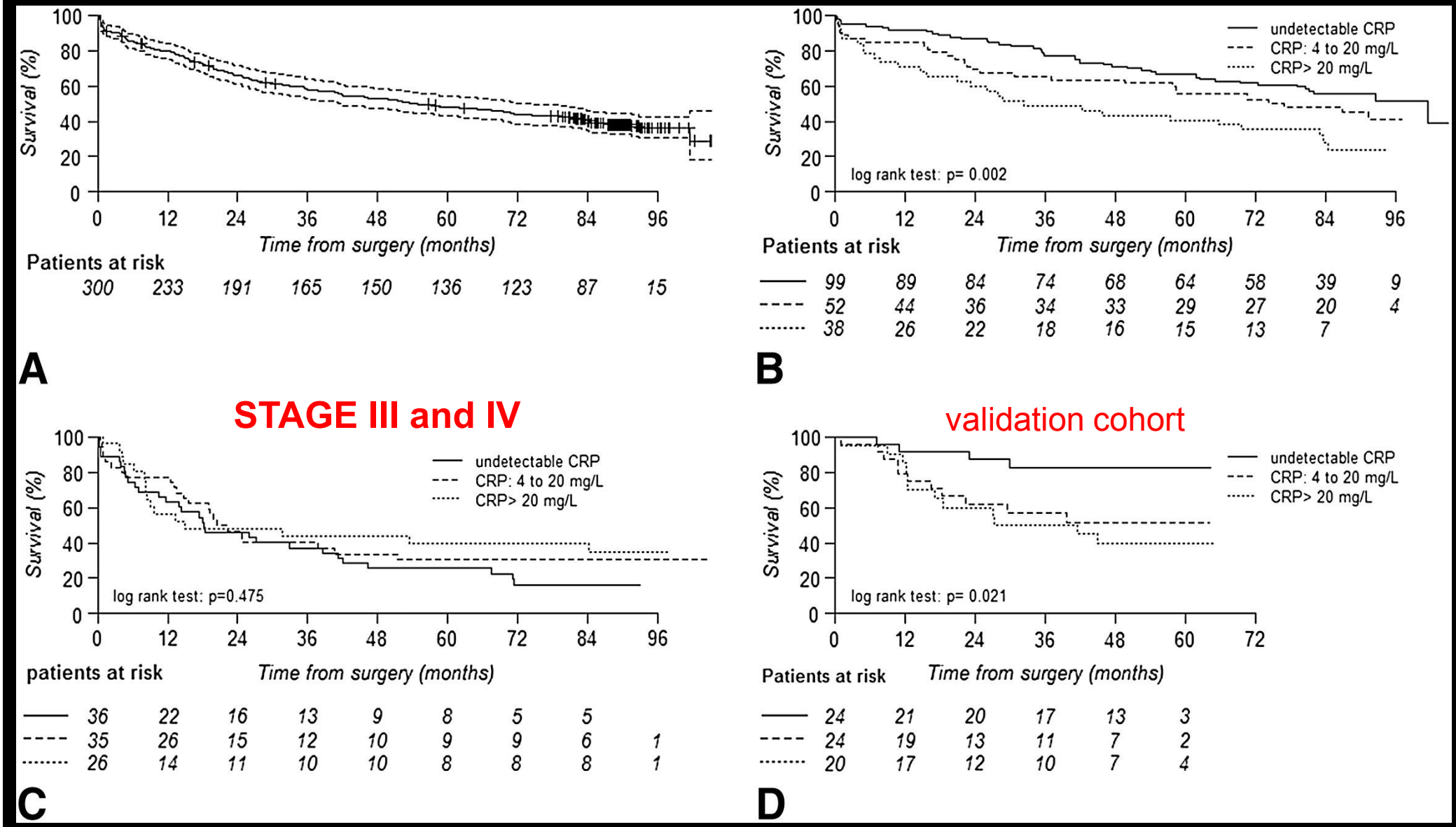
- Two emerging hallmarks of cancer:
  - Reprogramming of energy metabolism
  - **EVADING IMMUNE DISTRUCTION**
- Two enabling characteristic:
  - **INFLAMMATION**
  - Genome instability
- Recognition **Tumoral Microenvironnement**

Pre-resection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer.

Alifano et al, JTCVS 2011

- 300 patients operated on for non-small cell lung cancer
- CRP level was significantly associated with chronic bronchitis, hypoalbuminemia, pathologic stage, and peritumoral vascular emboli.
- Overall, 5-year survivals in whole population:
  - preoperative CRP 3 mg/L or lower > 55.6%
  - between 4 and 20 mg/L > 45.6%
  - greater than 20 mg/L were > 40.0%

Figure 1



The Journal of Thoracic and Cardiovascular Surgery 2011 142, 1161-1167DOI: (10.1016/j.jtcvs.2011.07.021)

Systemic Inflammation, Nutritional Status and Tumor Immune Microenvironment Determine Outcome of Resected NSCLC

Alifano M, Bobbio A. et al. PLoS ONE 9(9): 106914. ***2014***

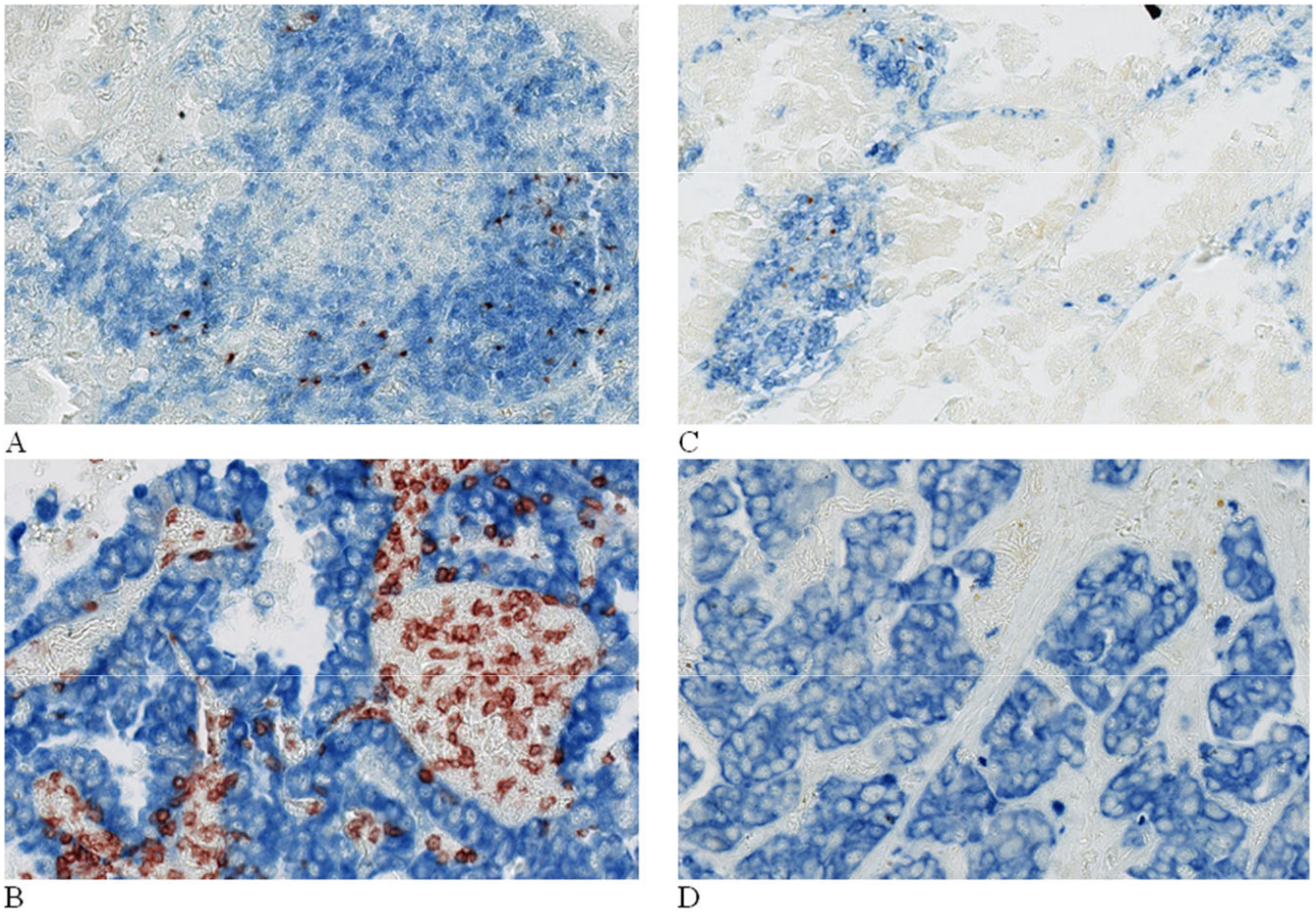
303 patients surgically treated for NSCLC

- **CRP** = SYSTEMIC INFLAMMATION
- **Pre-albumine** = NUTRITIONAL STATUS
- **Tumoral infiltration by**
  - **CD8+ Lymphocytes**
  - **Mature Dendritic Cells**

  = PRESENCE OF IMMUNITARY REPONSE IN MICROENVIRONMENT

CORRELATIONS WERE FOUND BETWEEN:

CRP, pre-albumine, and presence of dendritic cells in microenvironment

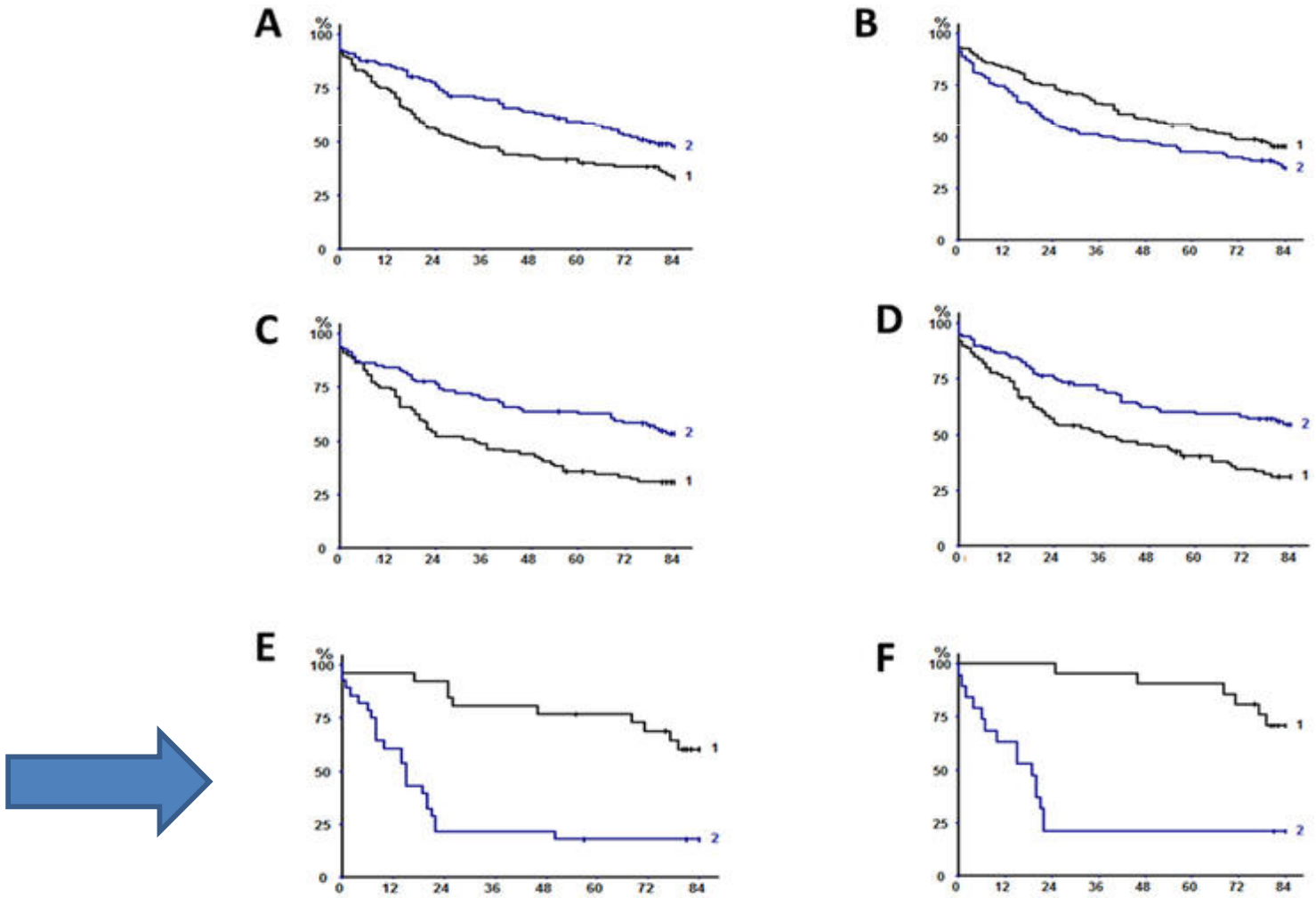


CD8+ and DC-Lamp+ cell densities. Magnification x 100

A) High density of DC-Lamp+ cells (red), these cells are located in CD3+ T-cell rich area (blue).

B) High density of CD8+ T cells (red) among pan-cytokeratins+ tumor nests (blue)

A) according to the prealbumin levels
B) according to CRP levels
C) according to CD8+ T cells density
D) according to mDC density
E) according to combination of CRP, prealbumin, and CD8 levels (≤3,>285 and>96 vs>3, <285 et <96) whole pop
F) according to combination of CRP, prealbumin, and CD8 levels (≤3,>285 and>96 vs>3, <285 et <96) Stage I et II



American Journal of
RESPIRATORY AND
CRITICAL CARE MEDICINE®

ATS Journals

INTRA-TUMORAL IMMUNE CELL DENSITIES ARE ASSOCIATED WITH LUNG ADENOCARCINOMA GENE ALTERATIONS

Mansuet-Lupo A & Alifano M. 2016 Jun 14. [Epub ahead of print]

MEASUREMENTS AND MAIN RESULTS:

In 282 tumors, we found 460 mutations, mainly in TP53 (59%), KRAS (40%), STK11 (24%), and EGFR (14%).

Intra-tumoral CD8+ T-cell density was high in smokers (P=0.02) and TP53-mutated tumors (P=0.02) and low in BRAF-mutated tumors (P=0.005).

Intra-tumoral mDC density was high with low pathological tumor stage (P=0.01) and low with STK11 mutation (P=0.004).

Finally, intra-tumoral CD8+ T-cell and mDC densities remained strong independent markers of overall survival (P= 0.001, P= 0.02, respectively.

CONCLUSIONS:

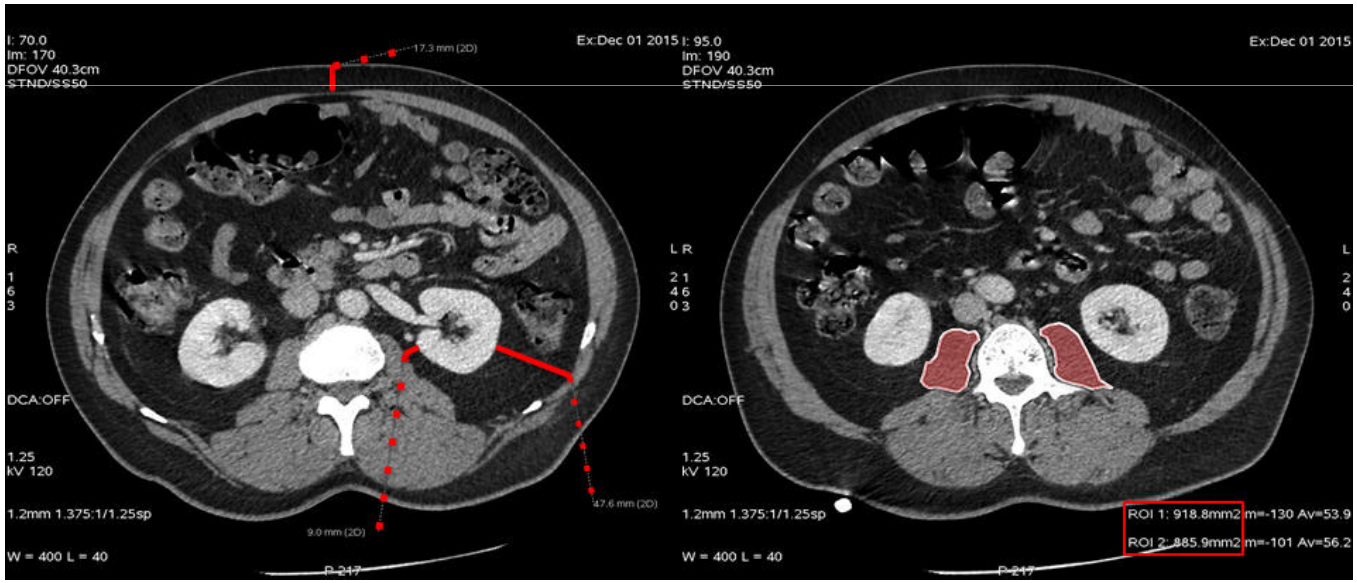
Intra-tumoral immune-cell densities (mDCs, CD8+ T cells, neutrophils, macrophages) were significantly associated with molecular alterations in adenocarcinoma underlying the interactions between cancer cells and their microenvironment

THE ANNALS OF THORACIC SURGERY
Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

Sarcopenia and Body Mass Index affect long term outcome in patients undergoing pneumonectomy for lung cancer

Hervechon M, Bobbio A et al. 2016 [Epub ahead of print]

- 161 PNEUMONECTOMIES
  - Body Mass Index
  - Total psoas area
    - SARCOPENIE = 33% of Total Psoas Area (CT en L3).
  - Perirenal fat
  - Subcutaneaous abdominal fat



- BMI and SARCOPENIE are correlated
- BMI is correlated with CRP
- SARCOPENIE is correlated with high CRP

BMI <25 kg/m2 (2) vs>25kg/m2 (1)

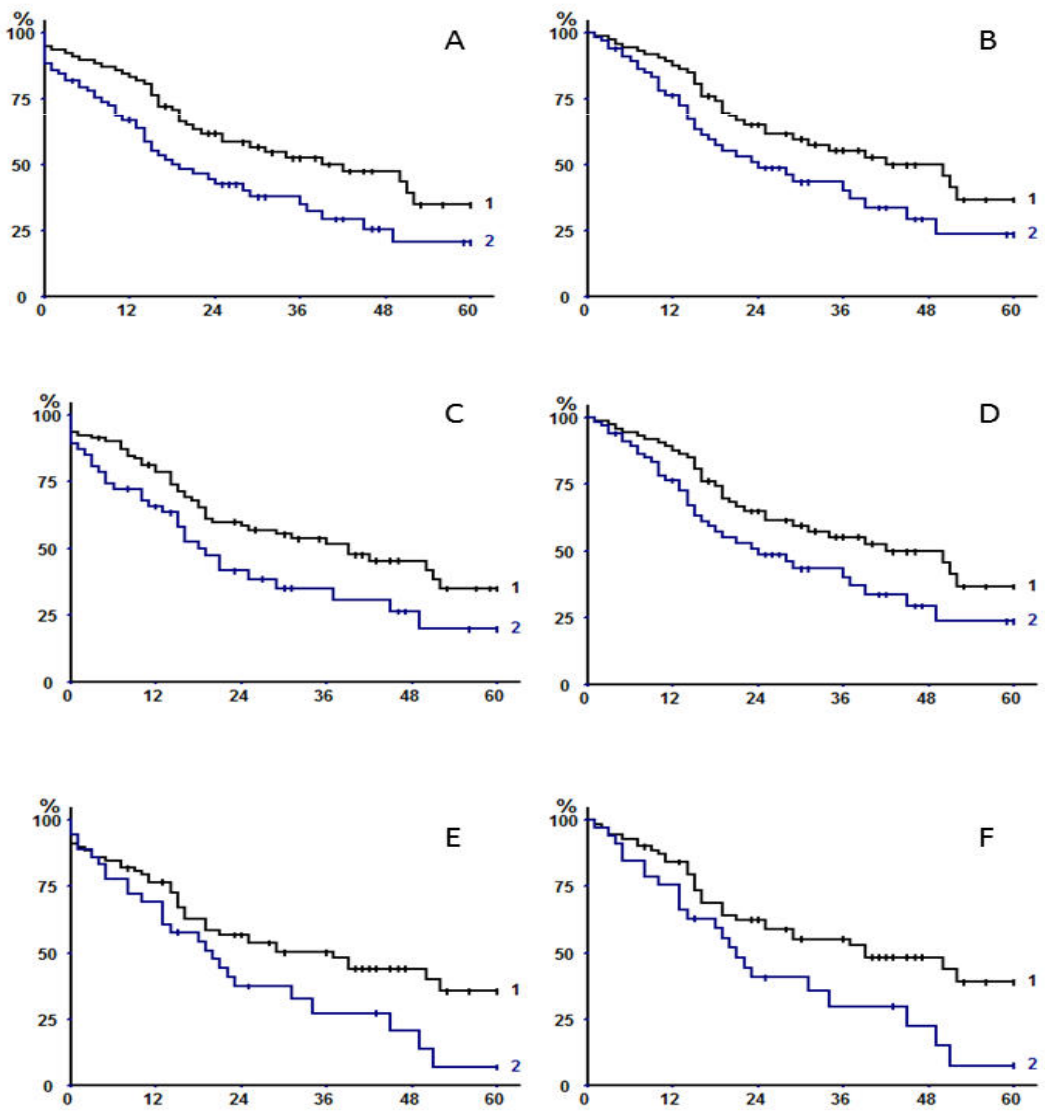
in the whole population (Panel A) and in operative survivors (Panel B), p= 0.015 and 0.037,

Total psoas area ≤33rd % vs >33rd %

in the whole population (Panel A) and in operative survivors (Panel B), p=0.029 and 0.048, respectively.

C-reactive protein ≤20mg/L (1) vs >20 mg/L

in the whole population (Panel A) and in operative survivors (Panel B), p=0.017 and 0.015, respectively.

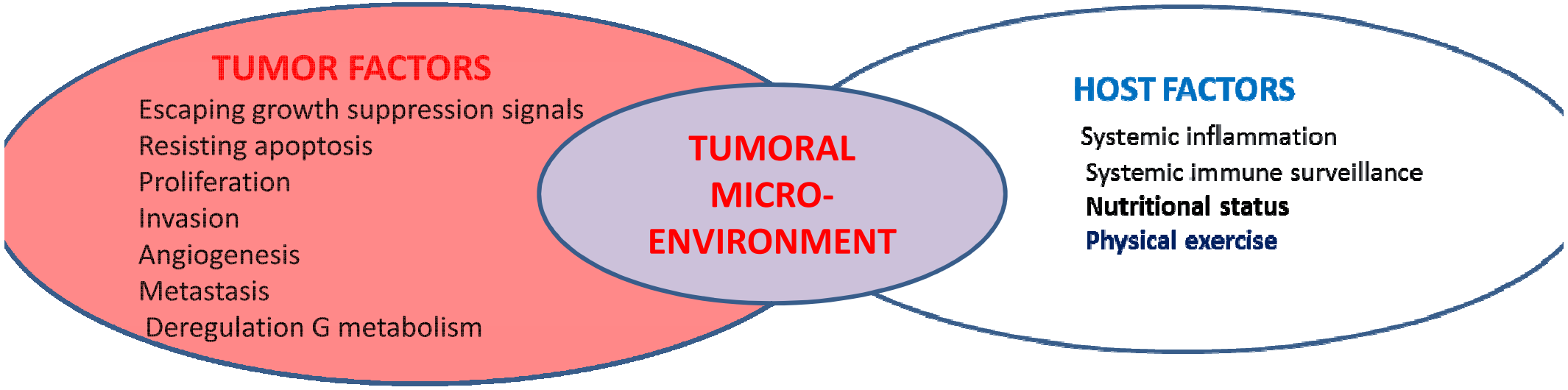


- Tumor must be seen as a biological based disease.

- Origin and development of cancer is related to cancer characteristic but also to host factors as well as to the their interaction.

- PROGNOSIS is scantly established only on anatomical presentation: the dogma of stage

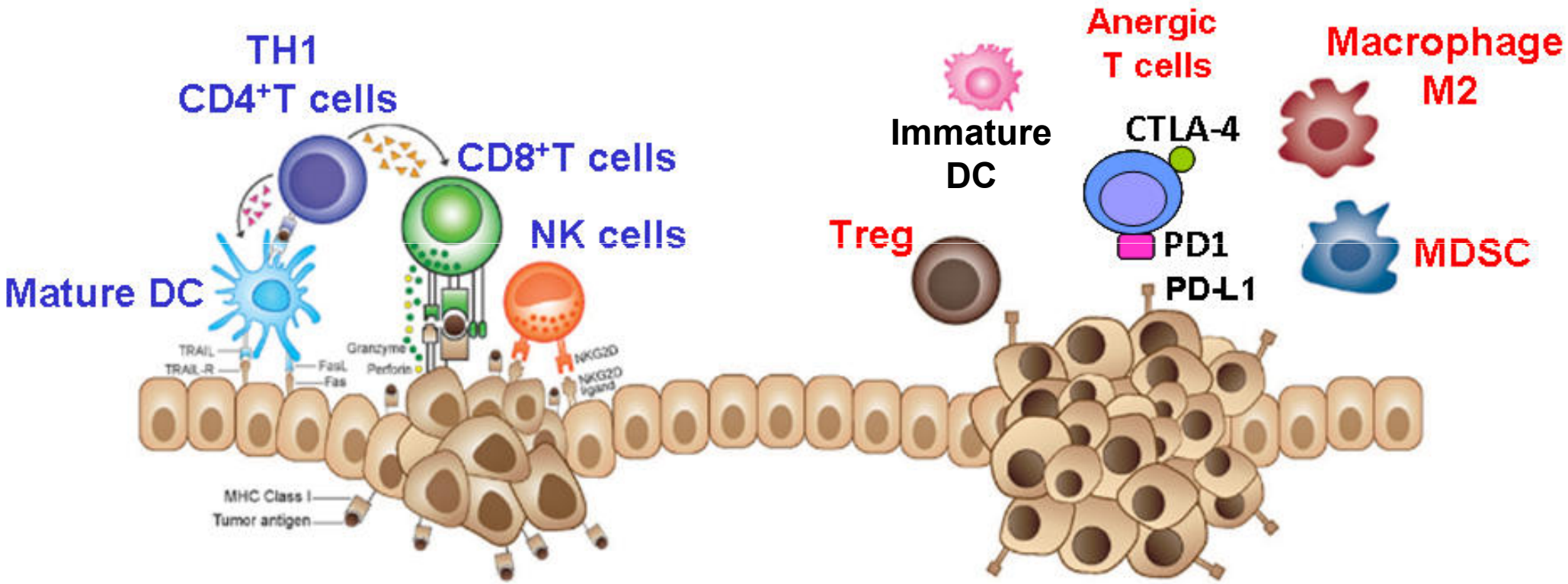
SURGERY OF OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER



IN 2011 BIOLOGICAL VISION OF CANCER DEVELOPMENT ET PROGRESSION INCLUDES FACTORS RELATED TO TUMOR CELLS, BUT ALSO FACTORS RELATED TO THE HOST AS WELL AS THEIR INTERACTION IN **MICROENVIRONNEMENT**

Bobbio A, Alifano M. Immune therapy of non-small cell lung cancer. The future. Pharm Research 2015; 99:217

In the tumors pro- and anti- tumoral cells are mixed and their relative number and function induce elimination, equilibrium or progression

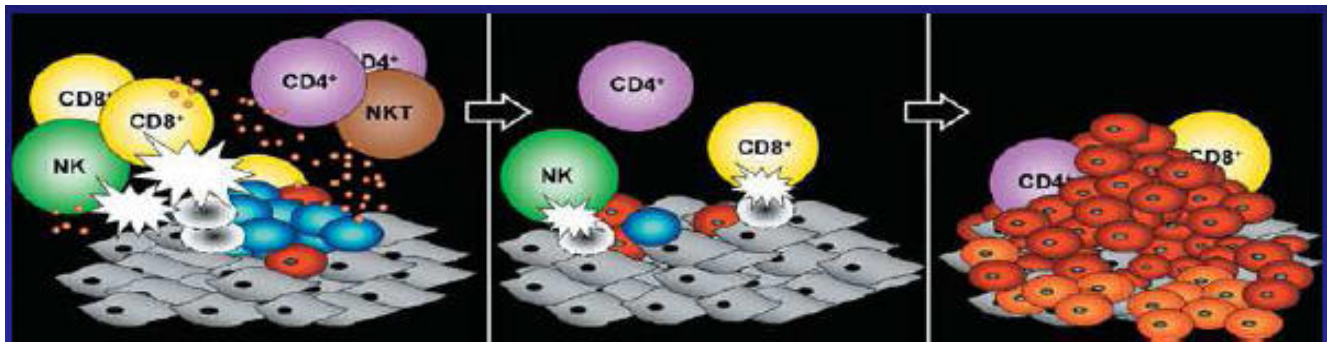


Anti-tumoral activity

equilibrium
dynamic

Pro-tumoral activity

Elimination
Immuno-surveillance



Escape

Monjazeb AM Front Oncol 2013

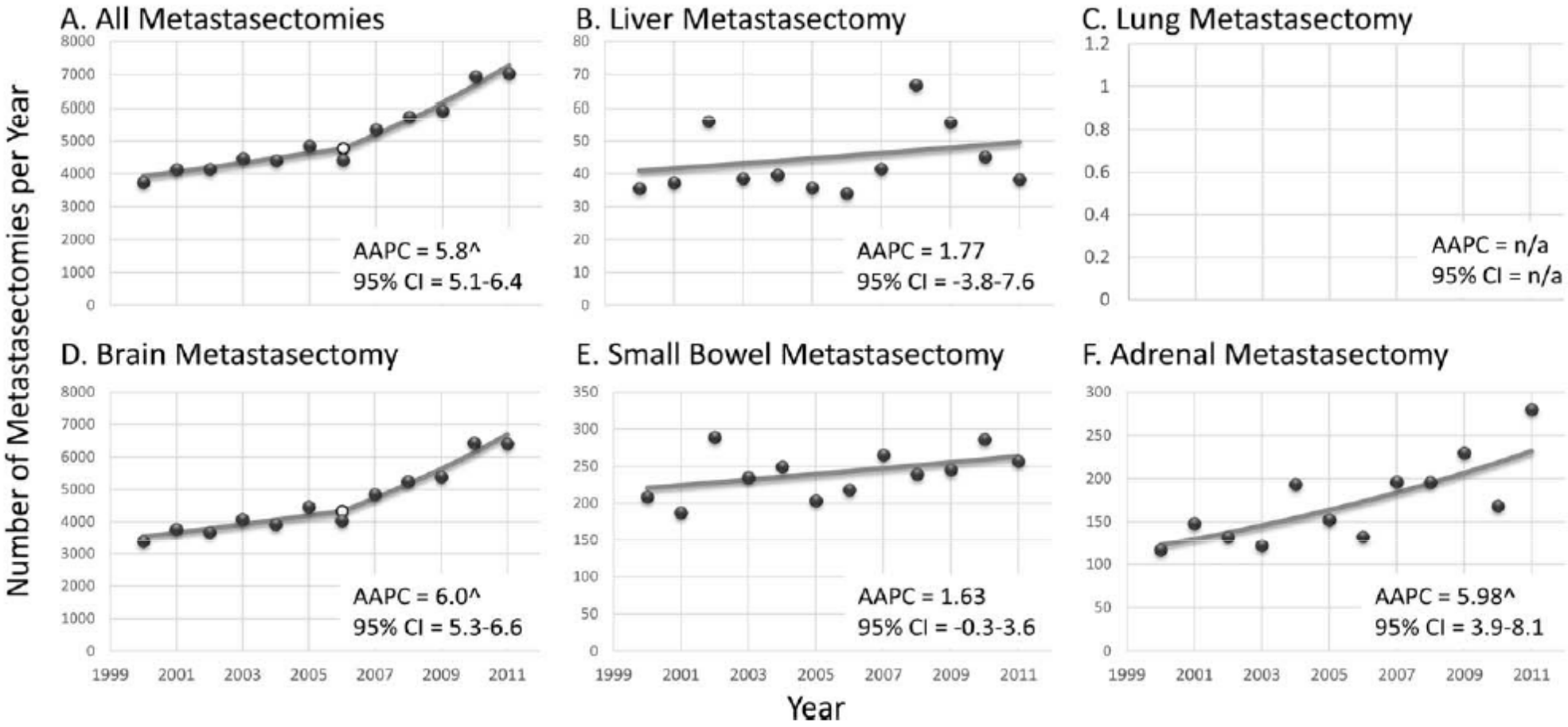
SURGERY OF OLIGOMETASTATIC NON-SMALL-CELL LUNG CANCER

- Historically, surgery for systemic disease was limited to palliation.

- Since 1980s several series reported prolonged survival following complete resection of primary tumors and oligometastatic disease in selected patients.

- The majority of patients considered for resection for CURE of metastatic NSCLC fall into three categories:
  1. those with homolateral or contralateral **lung disease**.
  2. those with localized metastasis to **the brain**.
  3. those with isolated **adrenal glands** metastasis.

The Rise in Metastasectomy Across Cancer Types Over the Past Decade (2001-2011). *Cancer* March 1, 2015



Based on **National Inpatient Sample** (NIS) **20% of all admission in US**.

Metastasectomy rates for lung cancer are shown for (A) all metastasectomies and (B) liver metastasectomy. (C) Lung metastasectomy was omitted. Rates are also shown for (D) brain metastasectomy, (E) small bowel metastasectomy, and (F) adrenal metastasectomy. AAPC indicates average annual percent change; , an AAPC that is significantly different from 0 (P<.05); 95% CI, 95% confidence interval; n/a, not applicable.

THE CASE OF LUNG METASTASECTOMY

LUNG METASTASECTOMY REGISTRY could not be fulfilled because no clear rules exist:

- for differentiating **synchronous** from **metastatic** tumor.
- for differentiating **synchronous** from **metachronous** tumors.
- for differentiating **metachronous** from **metastatic** tumors.

Classical criteria to define the same or different origin of lung nodules have been defined by Martini N in 1975

- *Based on 4 HISTOLOGIC TYPES on HES*
- *Low quality imaging*

Synchronous tumors

A. Physically separated tumors

B. Histology ***different***

identical **but in different segments, lobes or lungs, if**
no spread in lymphatic nodes common to either lesions
no extra pulmonary metastasis

Metachronous tumors

A. Histology ***different***

identical but **free interval between tumors > 2 years and**
second cancer in a different lobe or lung and
no spread in lymphatics common to either lesions
no extrapulmonary metastasis

Martini N et al. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12

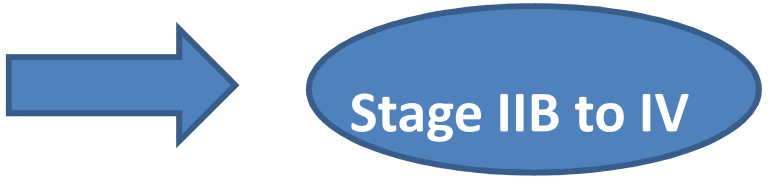
New insights

- **Pathological**
  - *Systematic Immuno-histochemistry*
  - *HISTO-PROGNOSTIC GRADES*
  - *Next Generation Sequencing Technology*

- **Imaging**
  - *Multi-row CT scan*
    - *Ground glass, mixed, solid lesions.*
  - *PET*

•In case of **nodules of identical origin** ambiguity in clinical and pathologic staging (TNM 2009):

- **T3**: same lobe
- **T4**: different homolateral lobe
- **M1a**: contralateral lobe



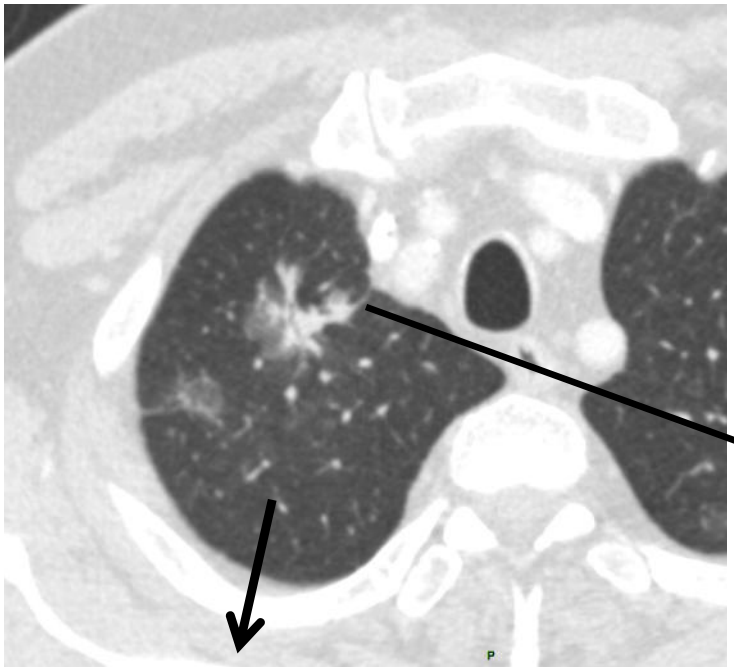
•**Controversies in the choice of treatment:**

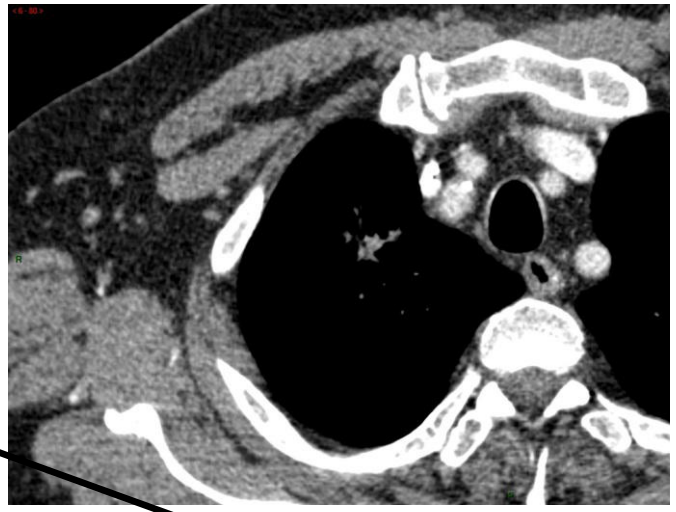
- Surgical vs Radiotherapy vs Chemiotherapy;

•**Surgical controversies:**

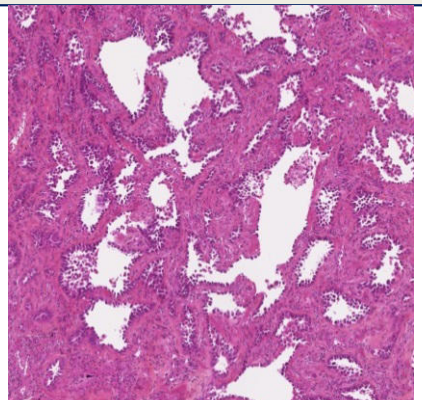
- **Extension of resection**
  - Dogma of lobectomy vs Segmentectomy
- **Surgical incision**:
  - Diatribes upon Conventional vs VATS vs ROBOTIC vs MONOPORTAL
- **Perioperative management**
  - Preoperative Rehabilitation Program
  - Enhanced Postoperative Recovery

CT semiology is a useful and poorly evaluated tool: Ground glass opacities and synchronous solid opacities

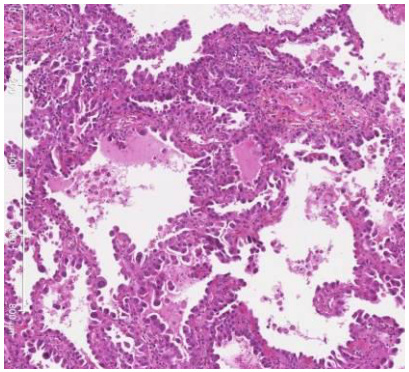




ADK tubular architecture



ADK papillary architecture

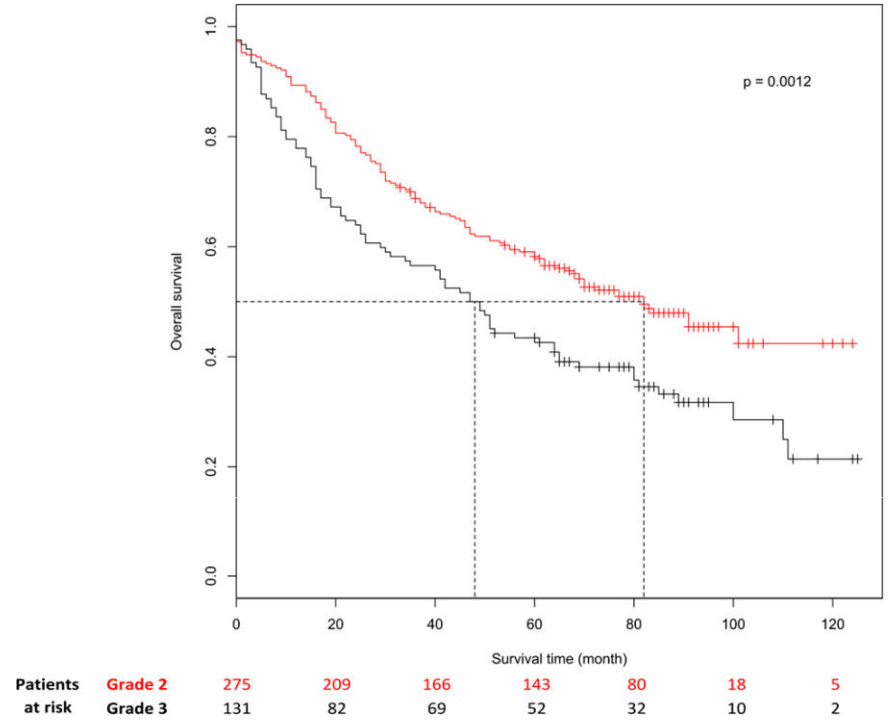


In the Martini classification same tumors

By means the IASLC classification two primary

CHEST JOURNAL
Official Publication of the American College of Chest Physicians

The new histologic classification of lung primary adenocarcinoma subtypes is a reliable prognostic marker and identifies tumors with different mutation status
Mansuet-Lupo A, Bobbio A, Blons H, et al. Chest . 2014;146(3):633-643.

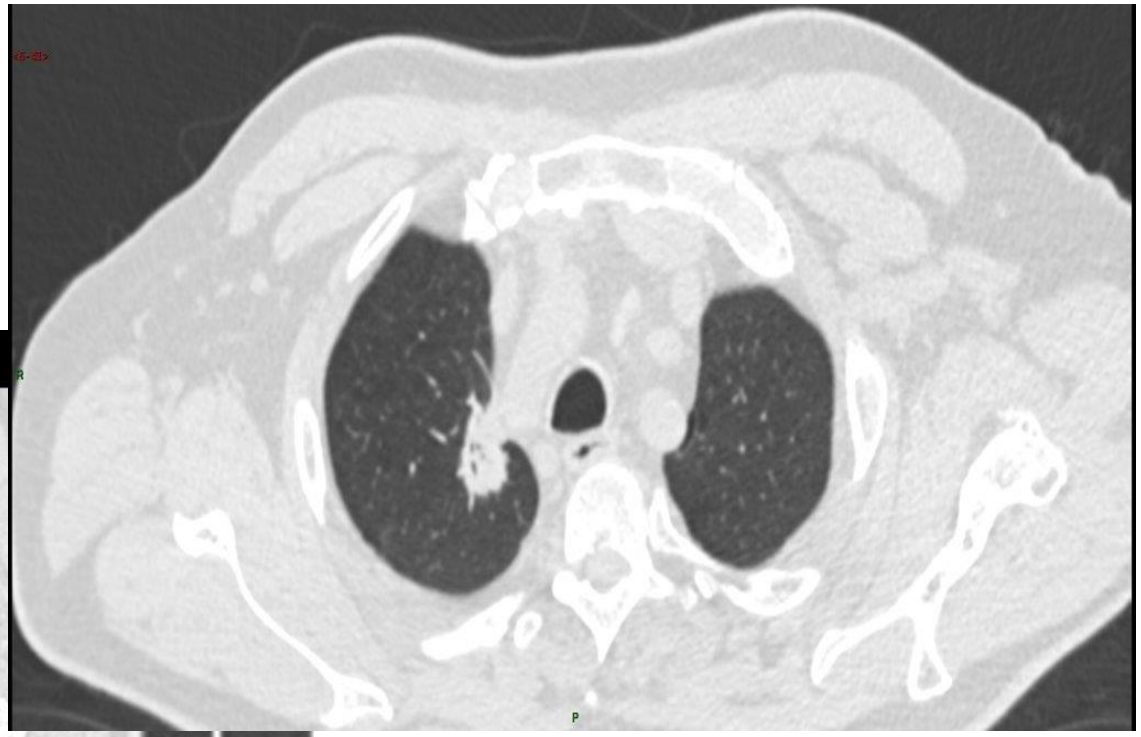


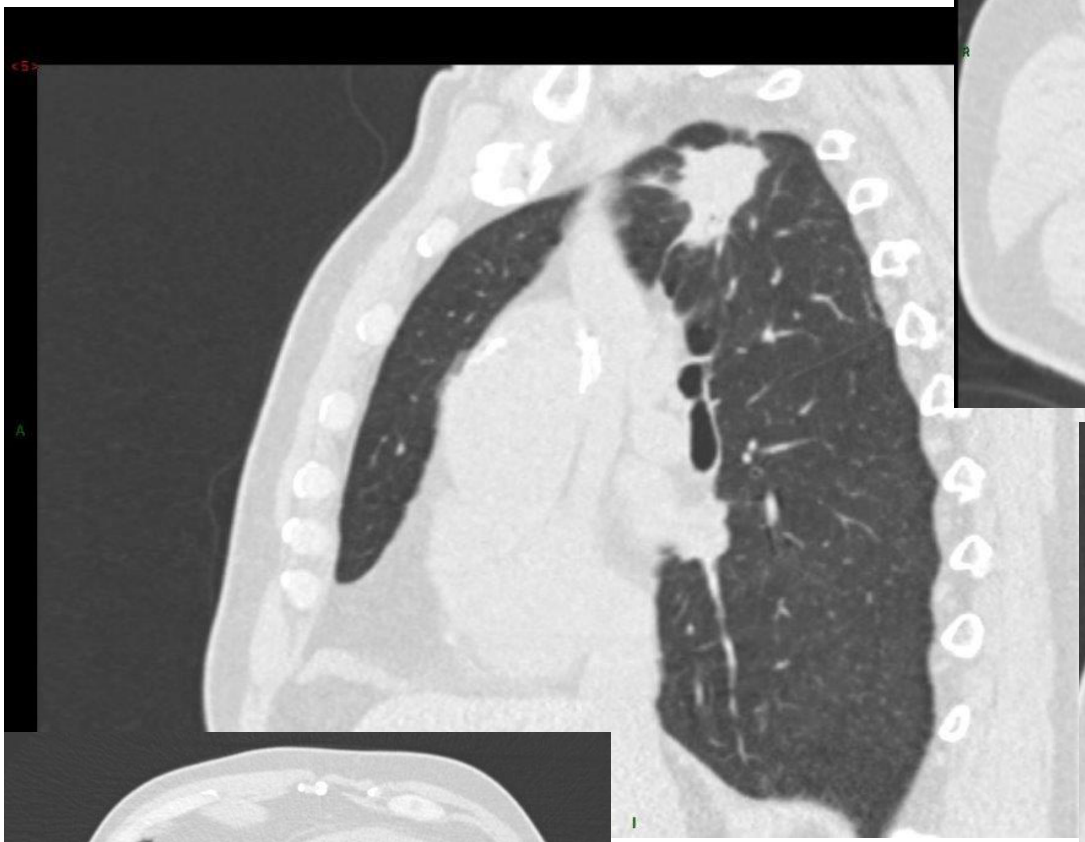
Evaluation of Histological subtype and Grade is a reliable method to differentiate synchronous primary Vs metastatic

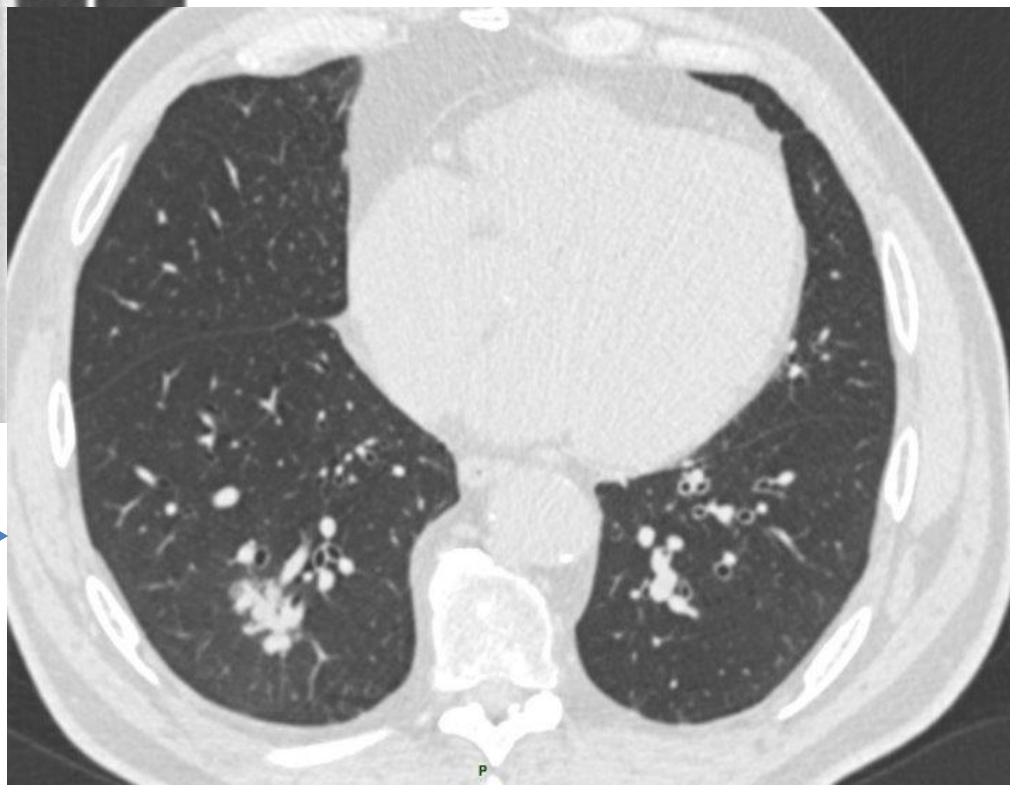
Synchronous homolateral tumors

M, 58 years 22 PA
3 right-sided lesions

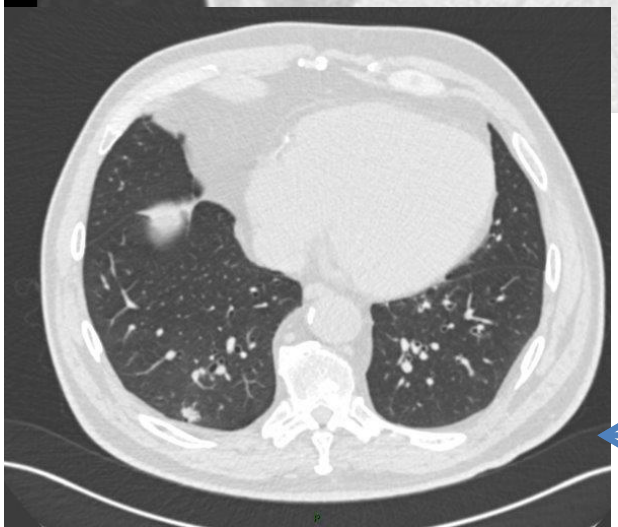
PET: SUV
Max 7.8







PET: SUV
Max 3.6



PET: SUV
Max 1.2

Role of PET in differentiating multiple tumors

Dijkman BG et al, Eur J Nucl Med Mol Imaging. 2010 Nov;37(11):2037-47

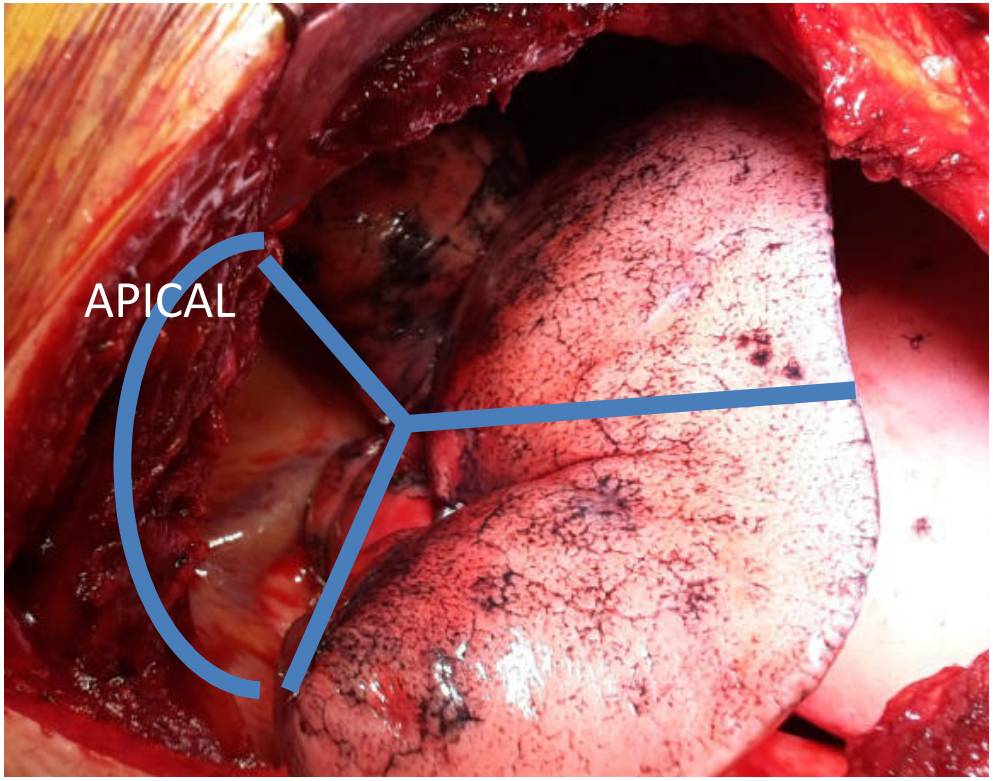
37 patients (21 metastatic disease, 16 second primary cancer) included for analysis.

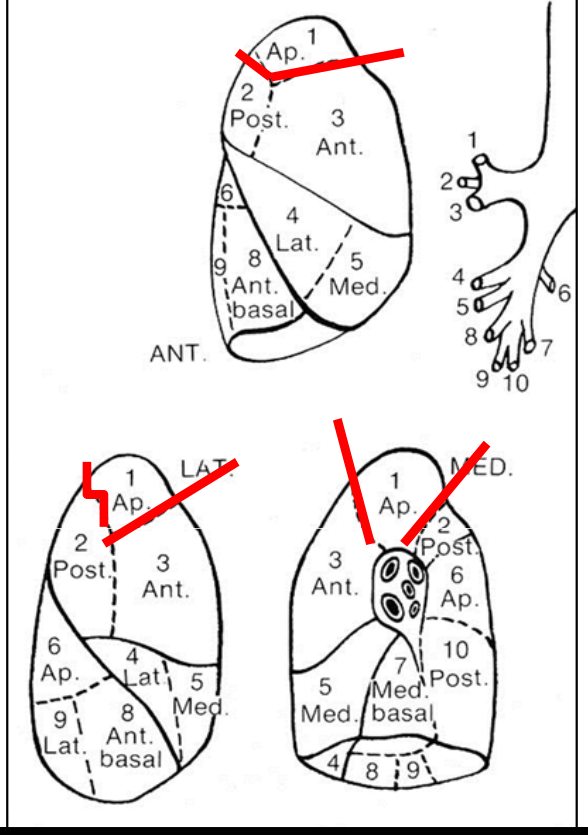
ΔSUV significantly higher in patients with second primary cancer than in those with metastatic disease (58 *vs* 28%, respectively, $p < 0.001$).

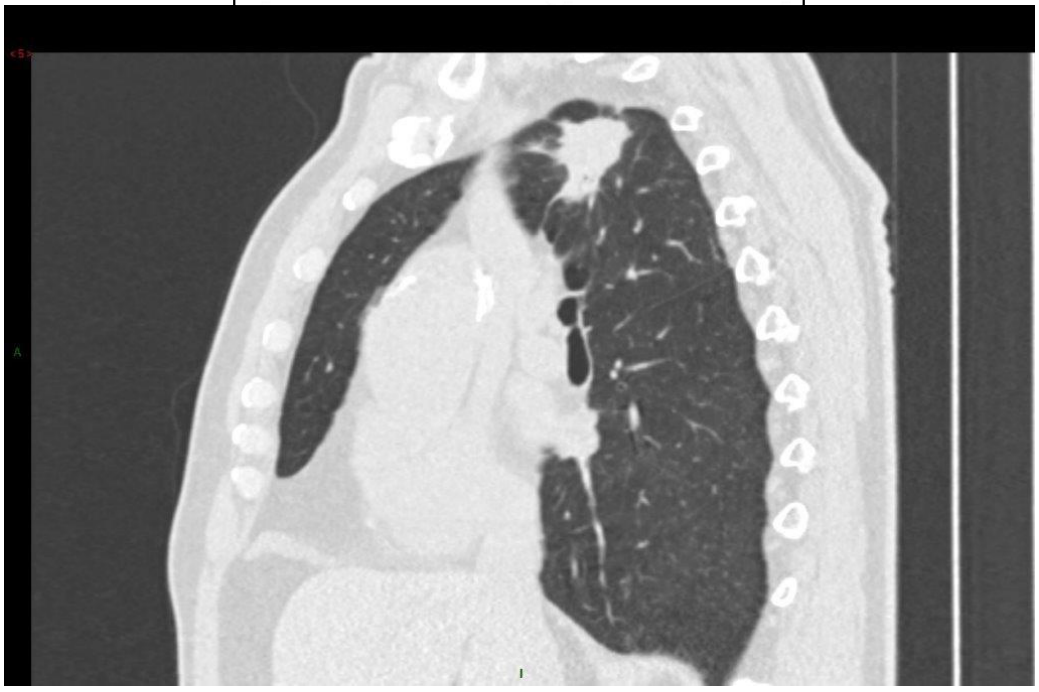
The area under the ROC curve was 0.81.

EX: 2 Lesions with SUV max of 12.1 and 3.5: (12.1-3.5)/12.1*100%=71%

APICAL ANATOMICAL SEGMENTECTOMY *(S1)*



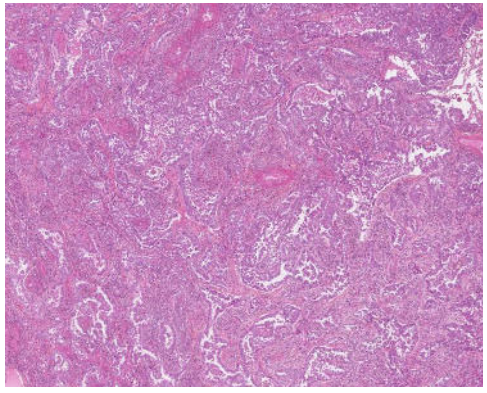




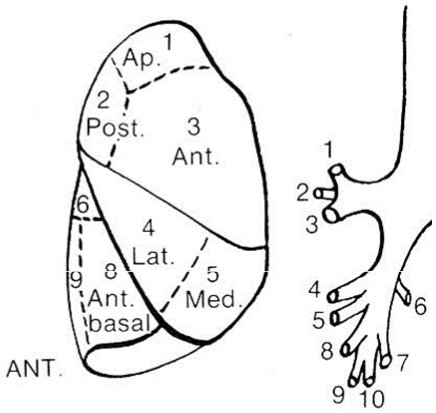
Tumor A

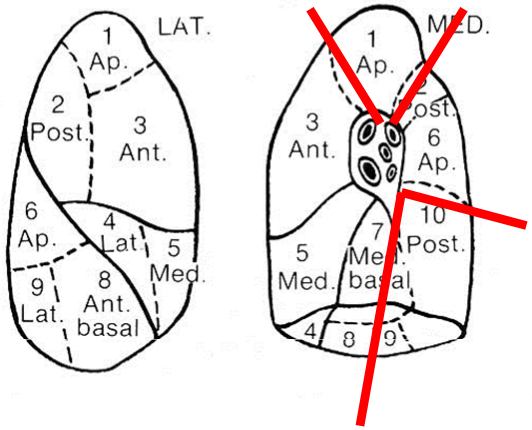
RUL **ADK tubular architecture**

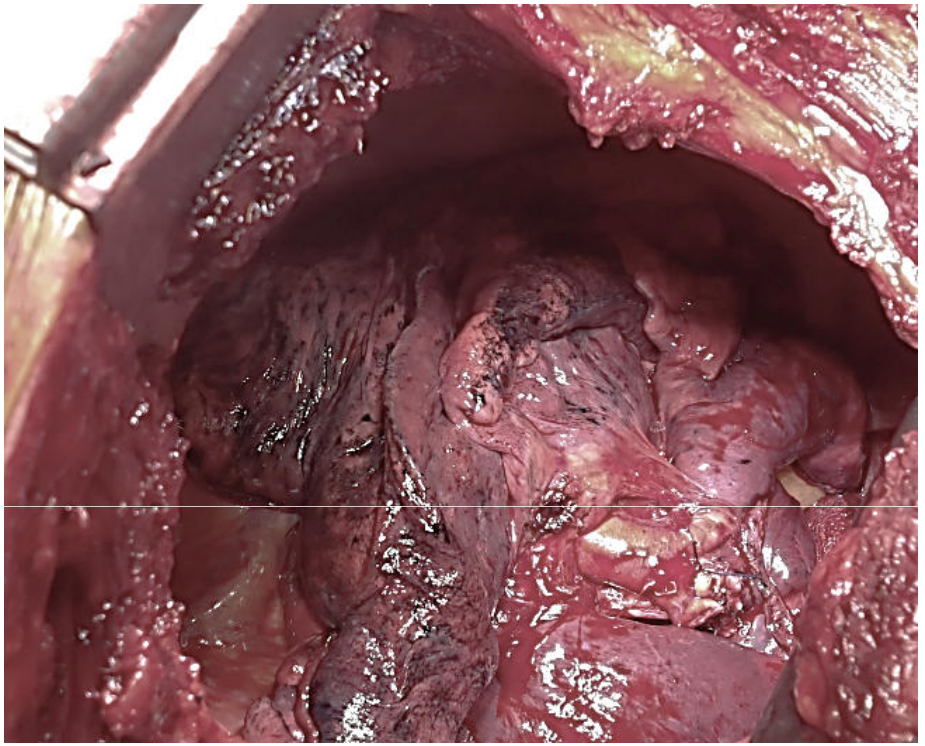
MOL BIOL: **KRAS +** (Mut c.35G>T, p.Gly12Val)

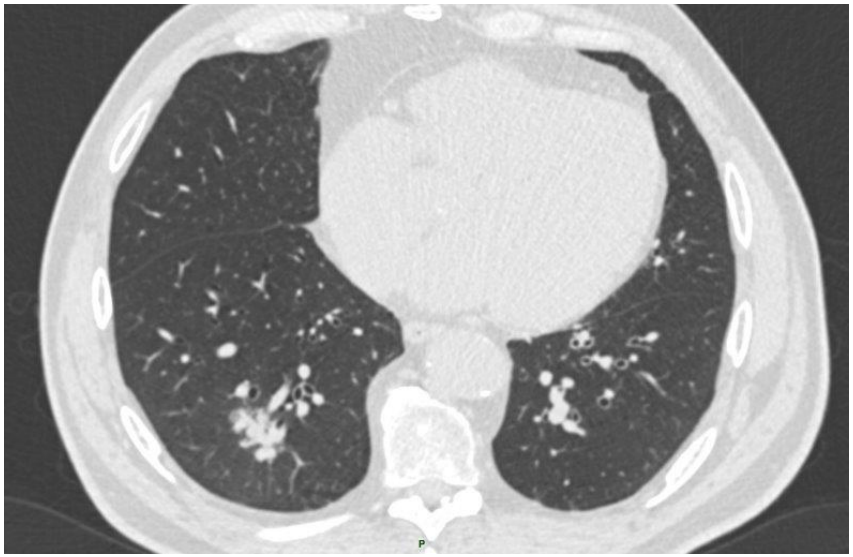


POSTERO MEDIO-LATERAL ANATOMICAL BISEGMENTECTOMY *(S9-S10)*









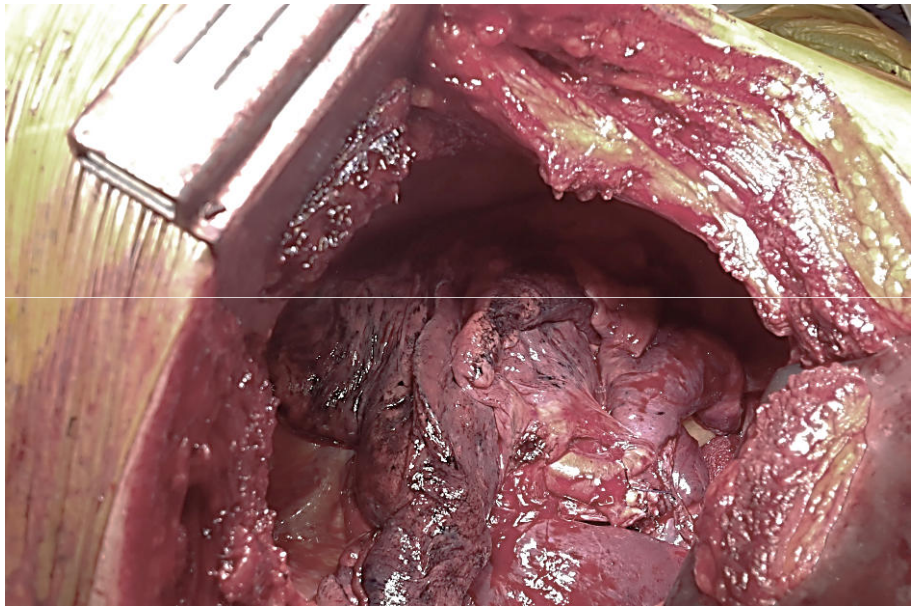
Tumor B

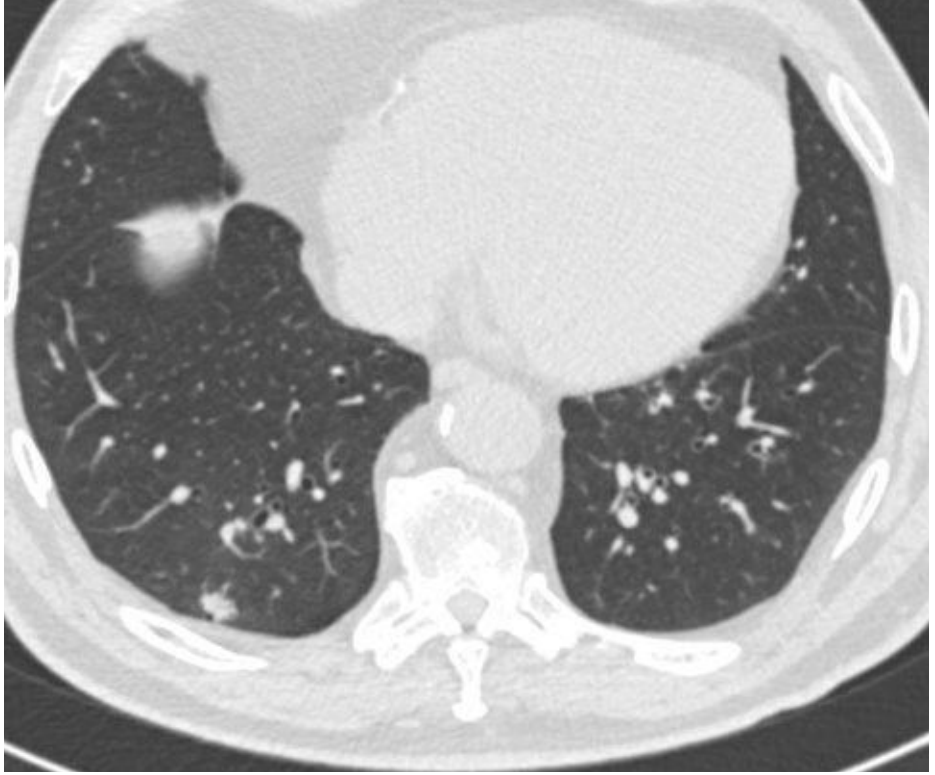
RLL **ADK papillary architecture**

MOL BIOL : **KRAS+ (**Mut **c.34 G>T**, p.GlyCys)

The two tumors have different histology and KRAS mutations : different tumors

POSTERO MEDIO-LATERAL ANATOMICAL BISEGMENTECTOMY *S9-S10*

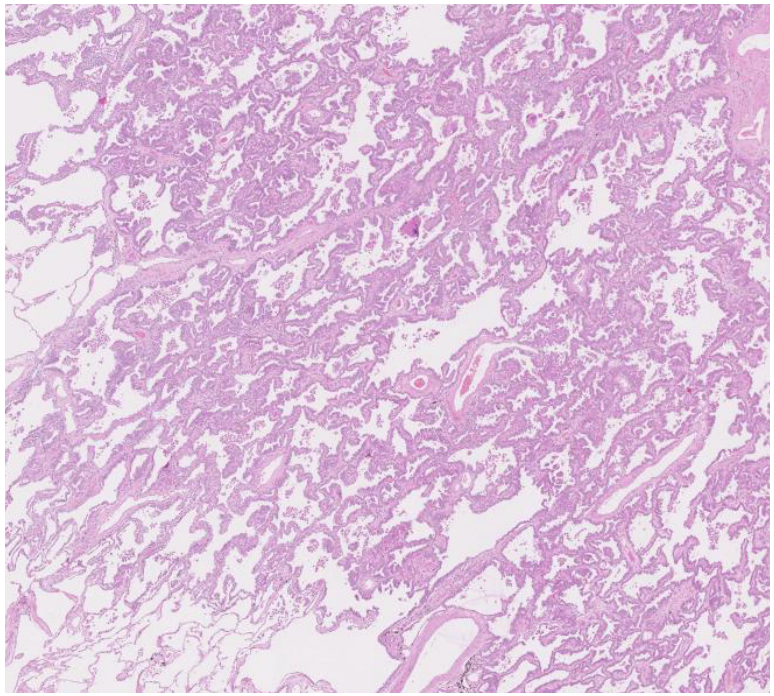




Tumor C

RLL **ADK papillary architecture**

MOL BIOL : **KRAS + (**Mut **c.34 G>T**, p.GlyCys)

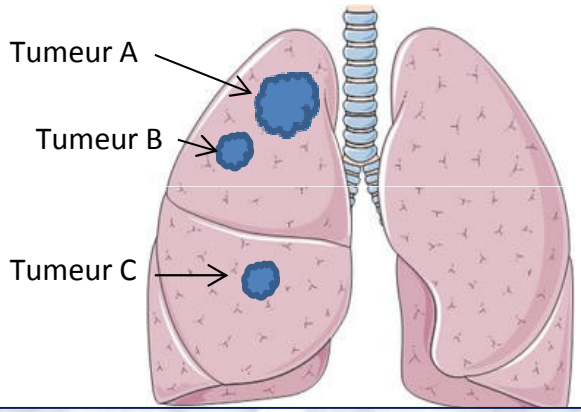


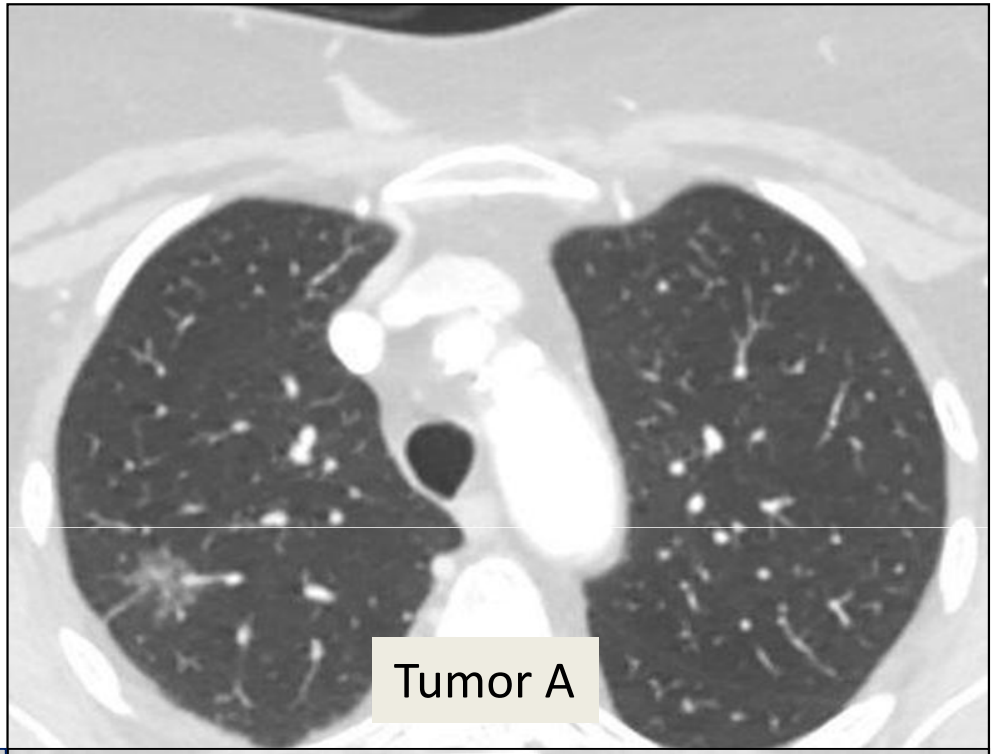
Apical tumor has a different KRAS mutation
Than the two RLL tumors, which are identical

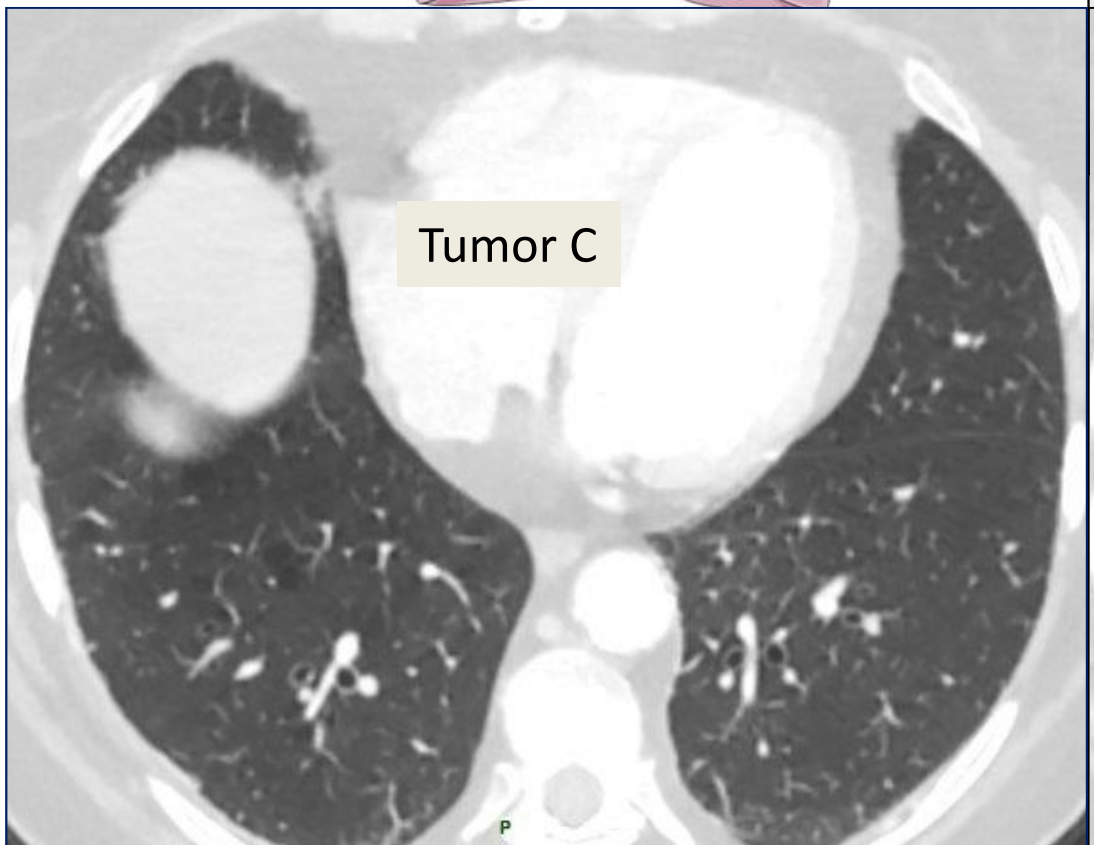
So : **T2aN0 for apical tumor**
T3N0 for RLL tumor

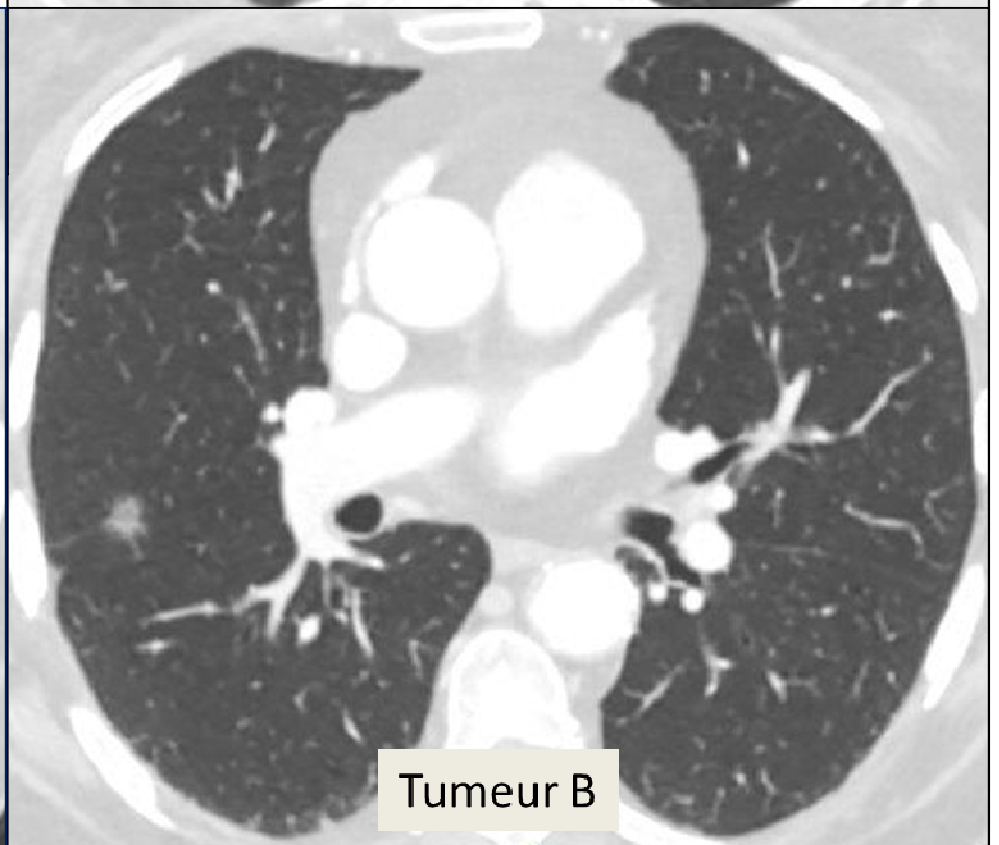
Synchronous homolateral tumors

W, 46 years, tobacco=0
« Casual » discovery of three nodules

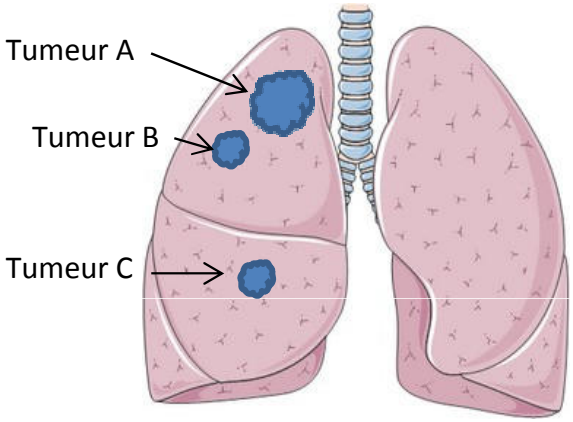


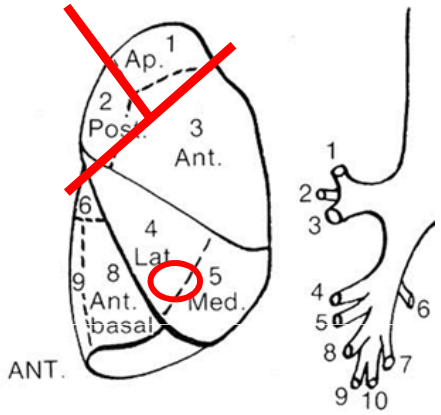


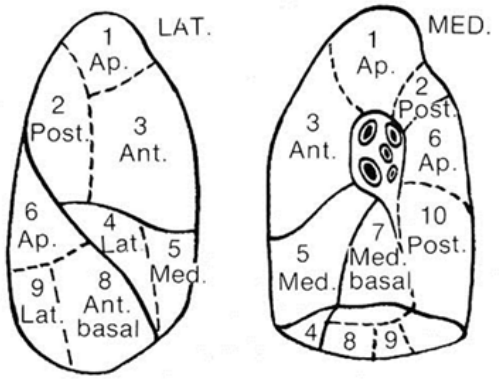




Treatment: anatomical bi-segmentectomy *(S1-S2)* and wedge ML







HISTOLOGY

Tubular adk, same morphology, in the 3 tumors:

- Apical segment : A: 1,8 cm (**ground glass**)
- Dorsal segment : B: 0,8 cm
- Middle lobe: C: 0,6 cm

pTNM (2009): pT4N0

Oncogenetic

CONCLUSION :
Interprétation des résultats en l'état actuel des connaissances :

Ces résultats indiquent qu'il s'agit de deux ou trois tumeurs indépendantes :

1- Présence de la mutation activatrice **p.Gly12Cys de KRAS** dans l'ADN extrait du bloc 11 (lésion 1,8 cm segment apicodorsal LSD) **A**

2 - Présence de la mutation activatrice **insertion exon 19 (p.Val738_Ile744dup) de l'EGFR**, dans l'ADN extrait du bloc 6 (lésion LMD). Ce type de mutation est rare (<1% des mutations), mais il a été montré qu'elle est activatrice et sensible aux TKI –EGFR (sensibilité afatinib supérieure au gefitinib) (He et al, Clin Cancer Res 2012). Il faut cependant noter que cette mutation est **très faiblement représentée** dans l'ADN étudié (3%), ce qui peut être en rapport avec une faible infiltration tumorale de la zone tissulaire macro-disséquée ou la présence de cette mutation dans un contingent sous-clonal minoritaire. Une réextraction de l'ADN de ce bloc a été demandée afin de préciser – si possible – l'interprétation de ce résultat. **C**

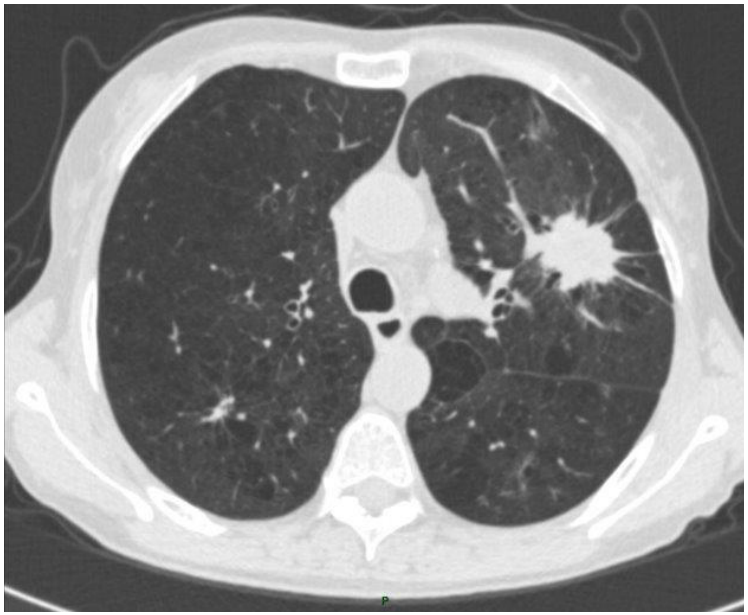
3 - Dans la limite des techniques utilisées, aucune mutation activatrice n'a été détectée au niveau des gènes BRAF, KRAS, PIK3CA et HER2 dans l'ADN extrait du bloc 16 (lésion 0,8 cm LSD). **B**

Aucun autre variant potentiellement oncogène n'a été détecté par l'analyse NGS du panel Oncomine solid tumor DNA kit.

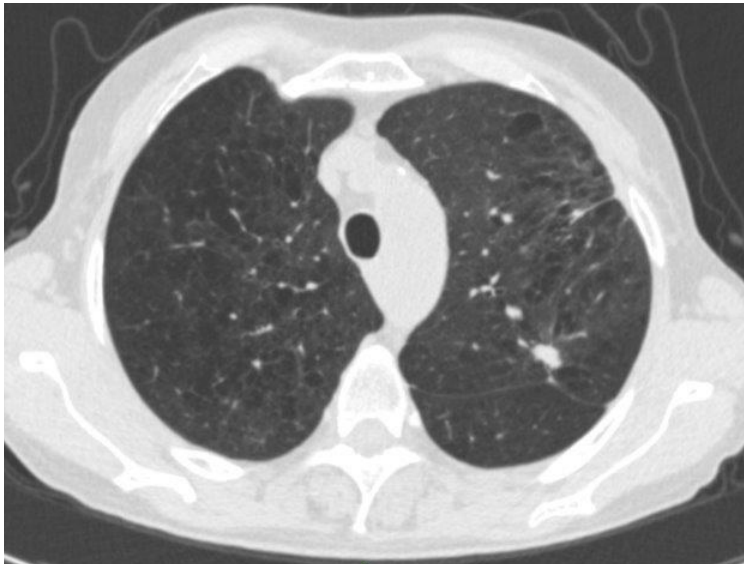
pTNM (2009): pT4N0 *or* 3 pT1N0

Bilateral synchronous tumors

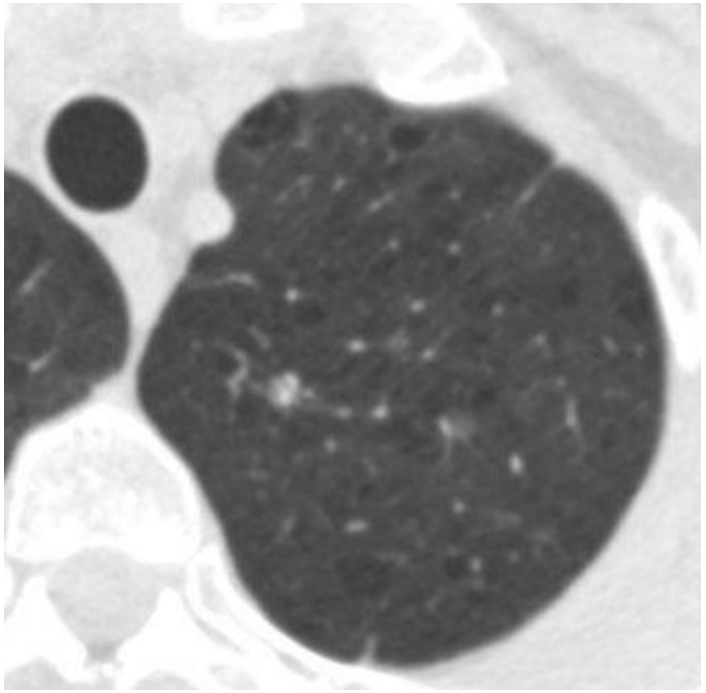
W, 58 years, tobacco, 60 PA
CT: multiple bilateral tumors, cN0 (PET: SUV MAX 1.6-8.0)
PET no mediastinal or hilar uptakeFEV1: 77%th;
Exeresis of cervical lesion: schwannoma
LEFT UPPER LOBECTOMY



Tumor A: ADK
Papillary=Intermediate Grade.
TP53+ pGlu 221 c,661G>T



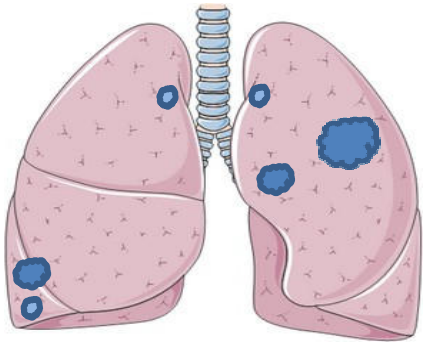
Tumor B: ADK
Solid = High-Grade
TP53 + pPro278,Leuc.833C>T



Tumor C: ADK
Lepidic, minimally invasive (MIA) = Low Grade
No MOL BIOL

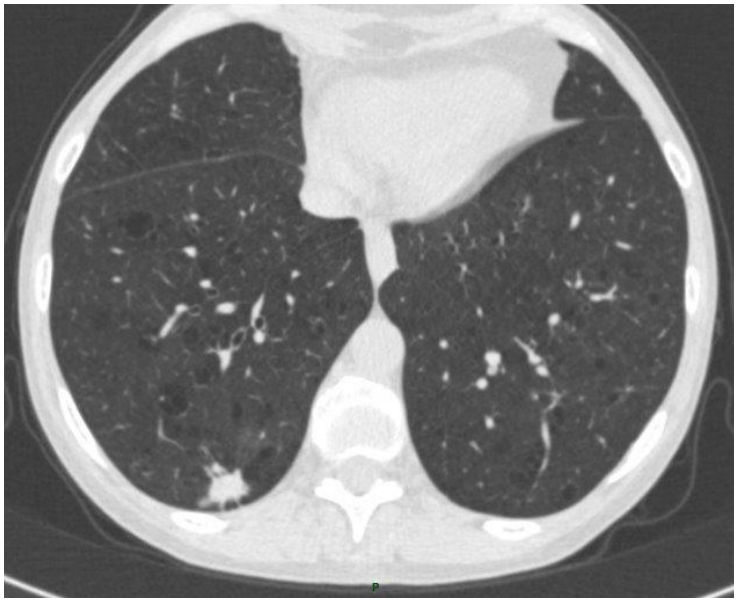
Different Histhology
Different Grade
Different Mutation

Bilateral synchronous tumors

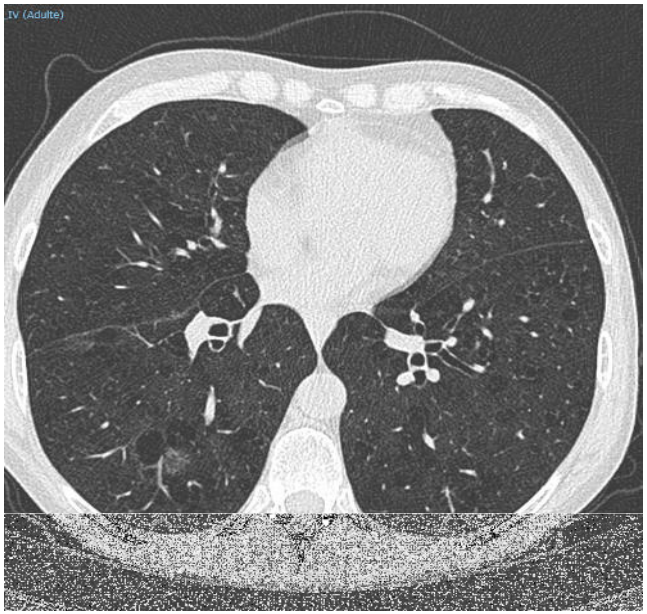


Spirometry after LUL: FEV1=78% predicted

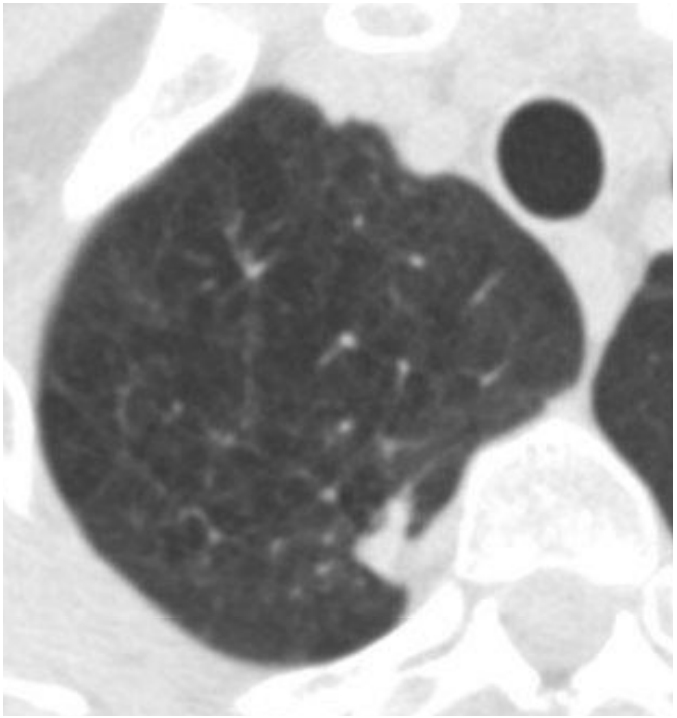
2nd time of surgical management :
Right lower lobectomy
Wedge right upper lobe



Tumor D:
ADK Solid = High Grade
KRAS + (c.34 G>T, p.Gly12Cys)
N+: 10, 11, 7, 8



Tumor E : MIA (low grade)



Tumor F :
ADK Tubular = Intermediate grade
KRAS + (c.34 G>T, p.Gly12Cys)

Same mutation KRAS TP53

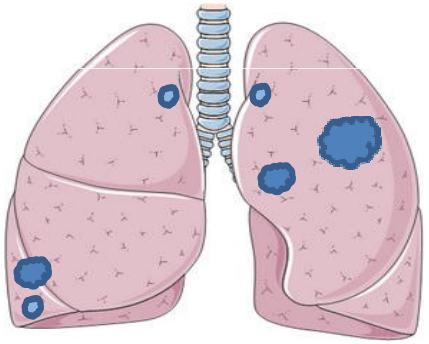
Oligometastasis or multiple lung tumors

Interesting research field, as new tools allow answering old questions

Clinical relevance (patients management), economic implications

From a practical point of view:

15-20 % of patients
Discovery at imaging



Surgery or Not

YES

EFFORTS TO DETERMINE:

- Primary
- Metastatic
- Clonal evolution

T1aN0 to M1aNx stage → **Major therapeutic impact**

NON

No histological proof,
No molecular or stromal evaluation,,,,

Follow-up

The case of metastasis to the adrenal gland and to the brain.

- The **adrenal gland** is a common site of metastatic disease in NSCLC, with involvement ranging from 18% to 42% in autopsy series.

- In the same setting **brain metastases** are found between 18% through 64% of patients with NSCLC.

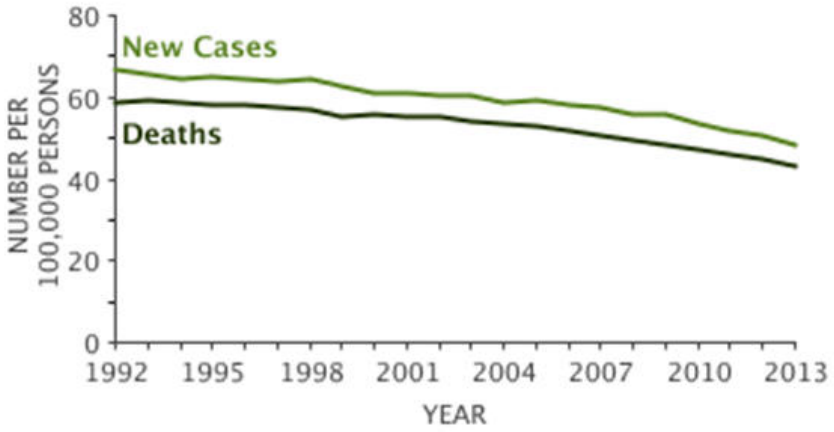
- The rate of **oligometastasis state** however is thought to be between **1.62% and 3.5% !**

Oligometastasis is a rare presentation of a common event

The case of metastasis to the adrenal gland and to the brain

- Incidence of NSCLC in U.S.

Estimated New Cases in 2016	224,390
% of All New Cancer Cases	13.3%
Estimated Deaths in 2016	158,080
% of All Cancer Deaths	26.5%



- "**Relative**" rare in face of the incidence of the disease
  - 1-3% = 2000 to 6000 new cases par year

http://seer.cancer.gov/statfacts/html/lungb.html

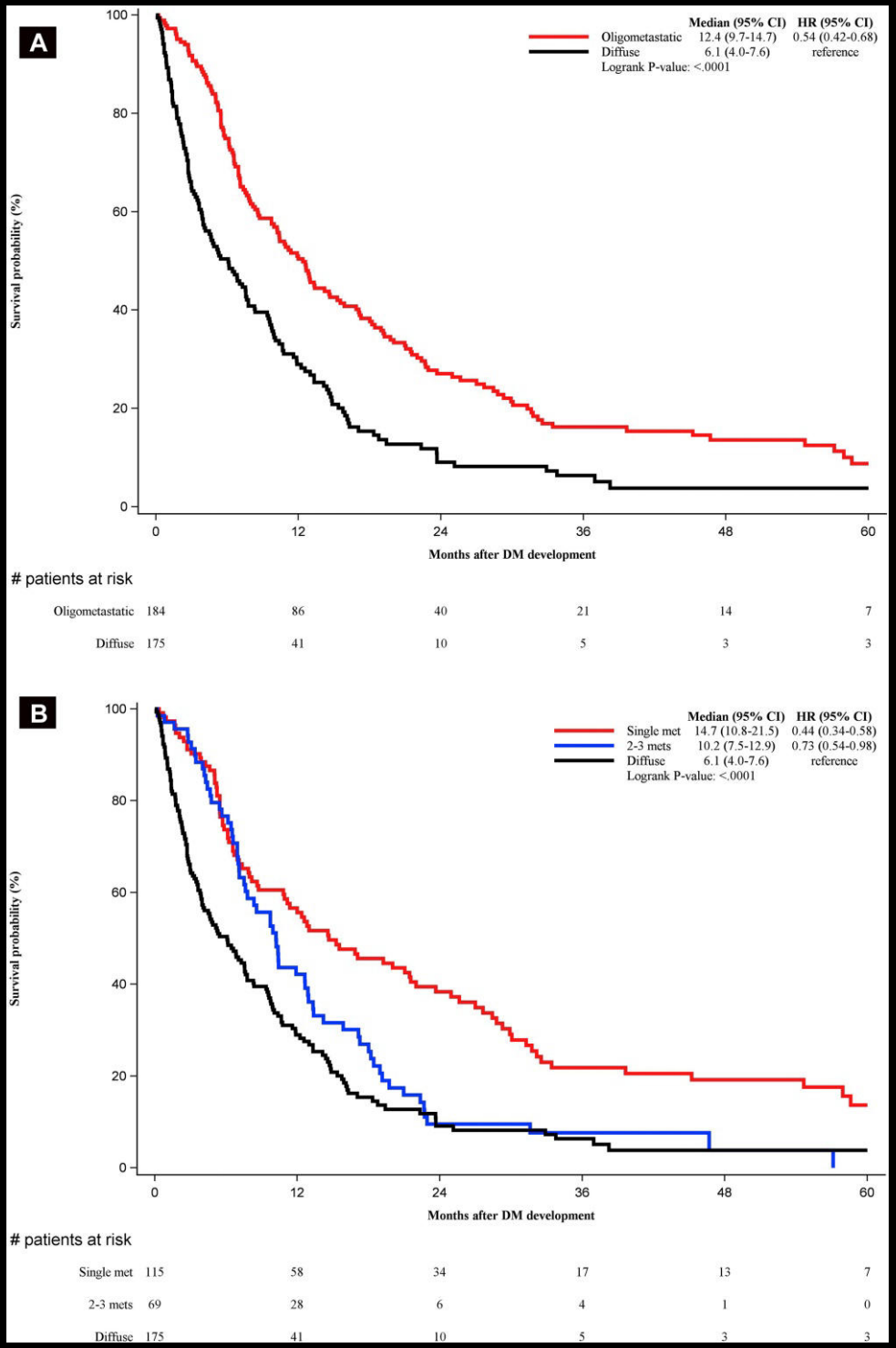
Patterns of Distant Metastases After Surgical Management of Non–Small-cell Lung Cancer

Jordan A. Torok, Lin Gu, Daniel J. Tandberg, Xiaofei Wang, David H. Harpole, Chris R. Kelsey, Joseph K. Salama

Clinical Lung Cancer
Volume 18, Issue 1, Pages e57-e70 (January 2017)
DOI: 10.1016/j.cllc.2016.06.011

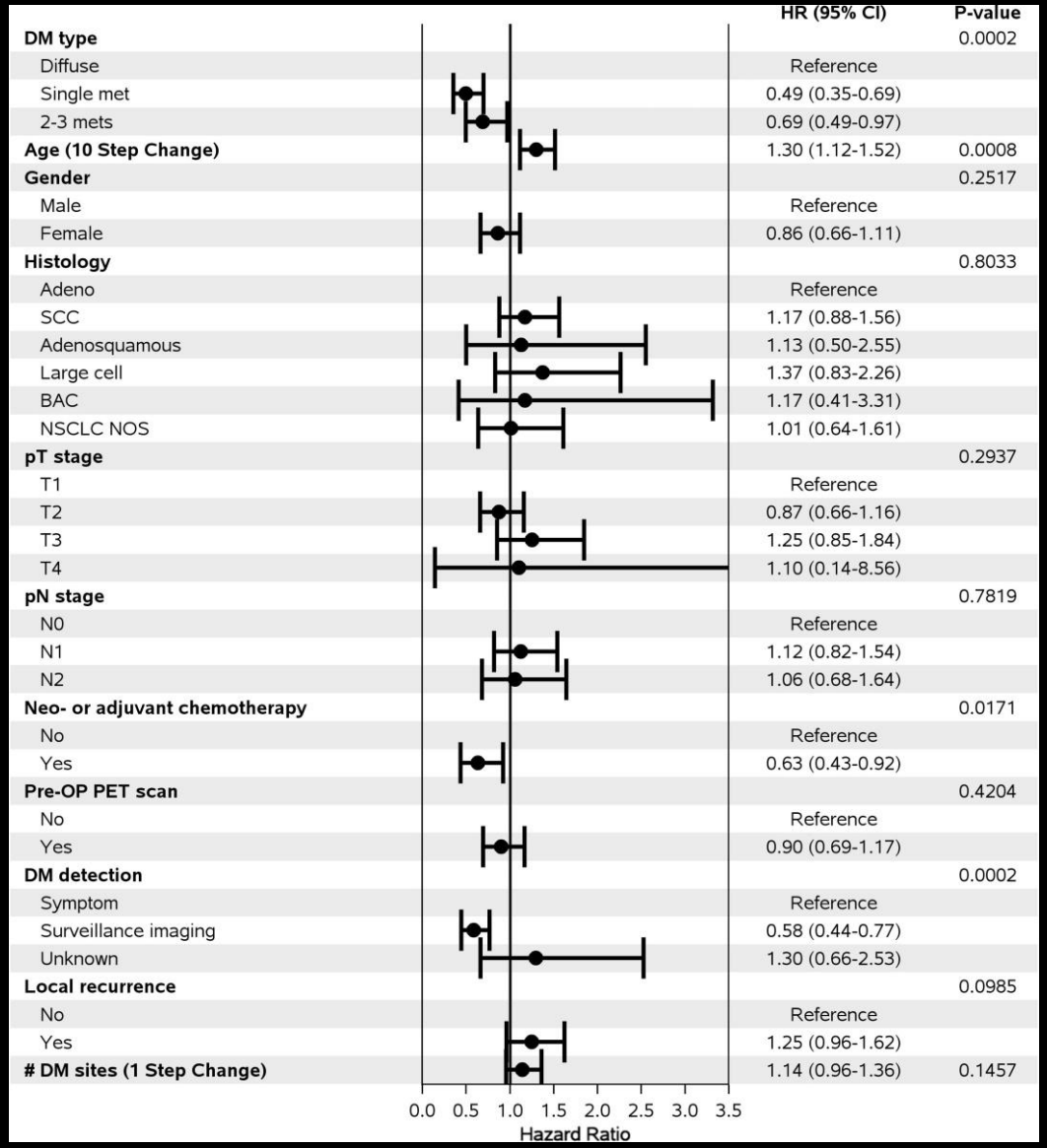
1719 patients reviewed
368 (21%) developed DMs with a median follow-up period of 39 months.
A single lesion was diagnosed in 115 patients (31%)
69 (19%) had 2 to 3 lesions (50% oligometastatic, 50% diffuse).

The median survival from the DM diagnosis for oligometastatic and diffuse DM was 12.4 and 6.1 months,



Clinical Lung Cancer 2017 18, e57-e70DOI: (10.1016/j.cllc.2016.06.011)

Figure 3



Clinical Lung Cancer 2017 18, e57-e70DOI: (10.1016/j.cllc.2016.06.011)

Solitary disease involving the **adrenal gland**

Study	No. Patients by Presentation			Survival influenced by presentation (S versus M)	Median Survival (months)	**5-Year Survival (%)**
	All	S	M			
Raz, et al. (2011)	20	12	8	No	19	34
Holy, et al. (2011)*	13				23	
Tanvetyanon, et al. (2008)*	114	48	66	Yes	S: 12M: 31	**S**: 26 **M**: 25
Mercier, et al. (2005)	23	6	17	No	13	23
Pfannschmidt, et al. (2005)	11	5	6	No	13	
Porte, et al. (2001)	43	32	11	No	11	7
Ambrogi, et al. (2001)	5	5	0			60
Beitler, et al. (1998)*	32	19	13	No	24	33

Solitary disease involving the **brain metastasis**

Study	No. Patients	by Nodal Stage			Survival influenced by N stage	Median Survival (months)	5-Year Survival (%)
	All	N0	N1	N2/N3			
Furak, et al. (2005)	19	9	2	8	No	19	24
Getman, et al. (2004)	16	8	3	5	No	9	19
Billing, et al. (2001)	28*	17	5	6	Yes	24	21
Bonnette, et al. (2001)	103*	40	23	36	No	12	11
Saitoh, et al. (1999)	24	11	3	10	No	7	8
Mussi, et al. (1996)	15	8	7*		Yes	18	7
Burt, et al. (1992)	65	27		30	No	21	16
Rossi, et al. (1987)	40	15	15	10	Yes	24	13
Magilligan, et al. (1986)	41				No		21

Retrospective case series of patients with surgically resected synchronous solitary brain metastasis from NSCLC

In the era of PET and MRI

1. Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival.

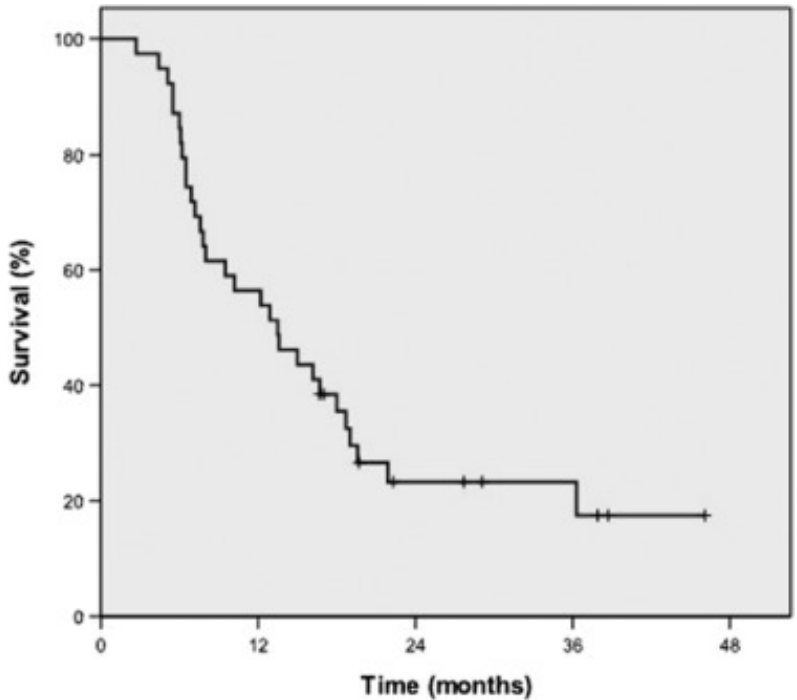
Gray PJ et al. Harvard Medical School, Boston, USA ***Lung Cancer***. *2014 Aug;85(2):239-44*

- Retrospective analysis of NSCLC patients between **1/2000 and 1/2011**
- 66 patients met all eligibility criteria, **38 of whom received AT** and 28 did not
- Actuarial 1-, 2- and 5-year survival for those
  - receiving ATT was 71%, 54% and **29%** respectively

2. Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases: Long-Term Results of a Prospective Phase II Trial (Nct01282450)

Dirk De Ruysscher, ***Journal of Thoracic Oncology***, Volume 7, 2012, 1547–1555

In this phase II study,**39 Pts** long-term PFS was found in a subgroup of NSCLC patients with synchronous oligometastases when treated radically. Identification of this favorable subgroup before therapy is needed.



Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases: Long-Term Results of a Prospective Phase II Trial (Nct01282450)

Dirk De Ruysscher, MD, PhD, Rinus Wanders, MD, Angela van Baardwijk, MD, PhD, Anne-Marie C. Dingemans, MD, PhD, Bart Reymen, MD, Ruud Houben, MSc, Gerben Bootsma, MD, PhD, Cordula Pitz, MD, PhD, Linda van Eijsden, MD, Wiel Geraedts, MD, Brigitta G. Baumert, MD, PhD, Philippe Lambin, MD, PhD

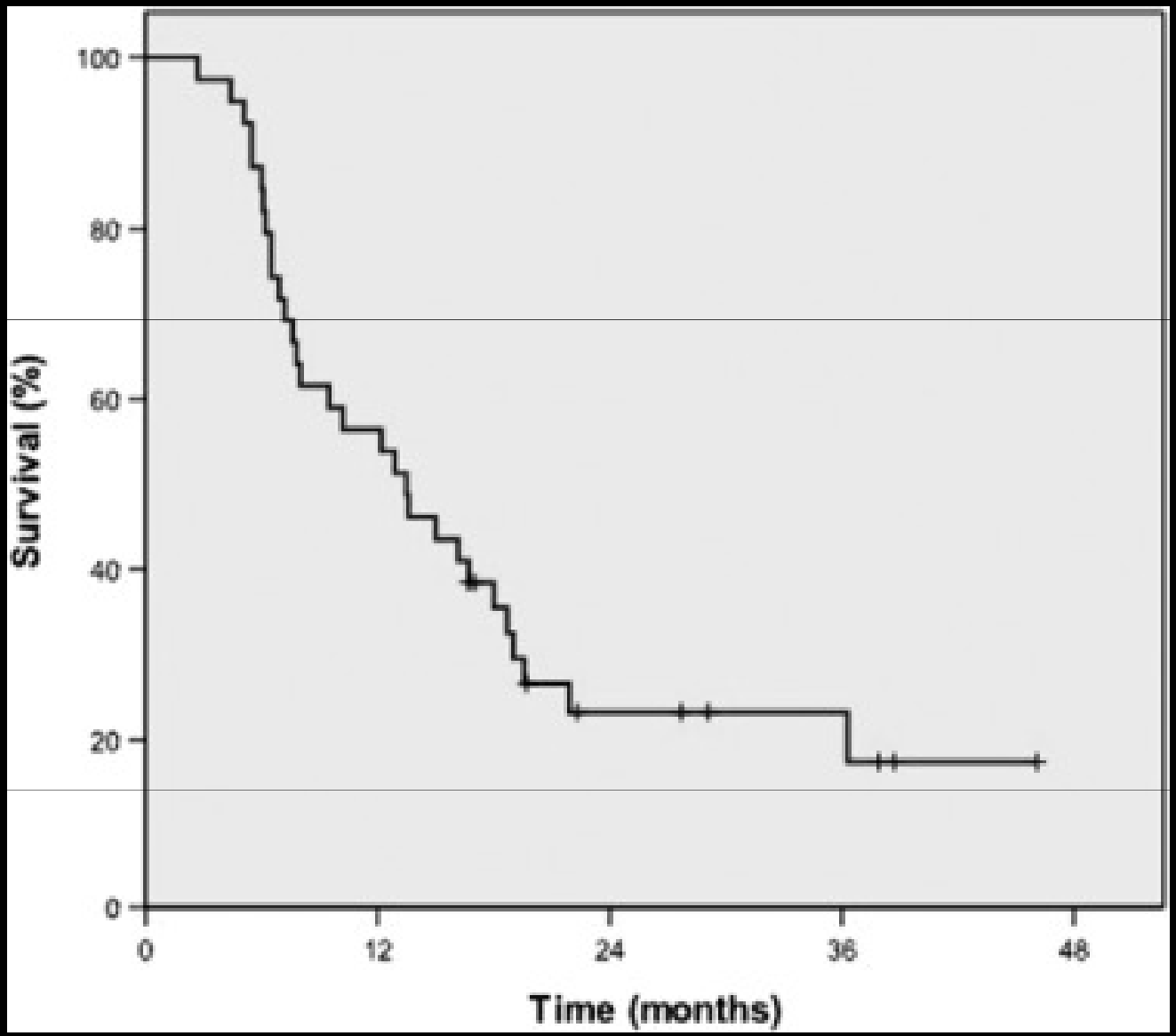
Journal of Thoracic Oncology
Volume 7, Issue 10, Pages 1547-1555 (October 2012)
DOI: 10.1097/JTO.0b013e318262caf6

40 patients enrolled
39 evaluable (18 men, 21 women); mean age 62.1 ± 9.2 years (range, 44–81).
29 (74%) had *local* stage III;
17 (44%) brain, 7 (18%) bone, 4(10%) adrenal gland metastases
35 (87%) had a single metastatic lesion.

Median overall survival (OS) was 13.5 months
1-, 2-, and 3-year OS was 56.4%, 23.3%, and 17.5%, respectively.

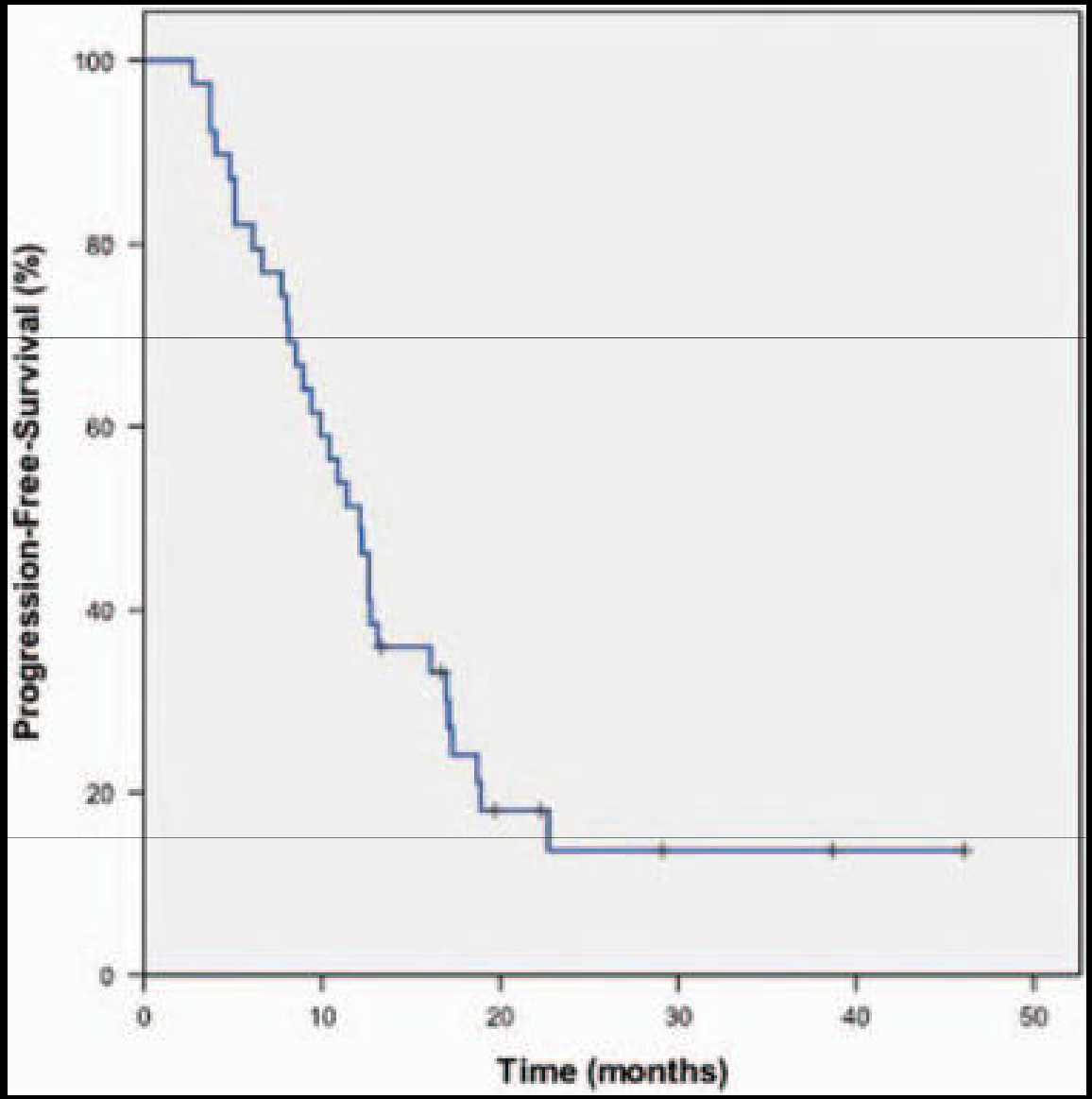
Median progression-free survival (PFS) was 12.1 months
1-year PFS was 51.3%, and both 2- and 3-year PFS was 13.6%.
Only two patients (5%) had a local recurrence.
No patient or tumor parameter, including volume and ^{18}F-deoxyglucose uptake was significantly correlated with OS or PFS.

FIGURE 1



Journal of Thoracic Oncology 2012 7, 1547-1555DOI: (10.1097/JTO.0b013e318262caf6)

FIGURE 2

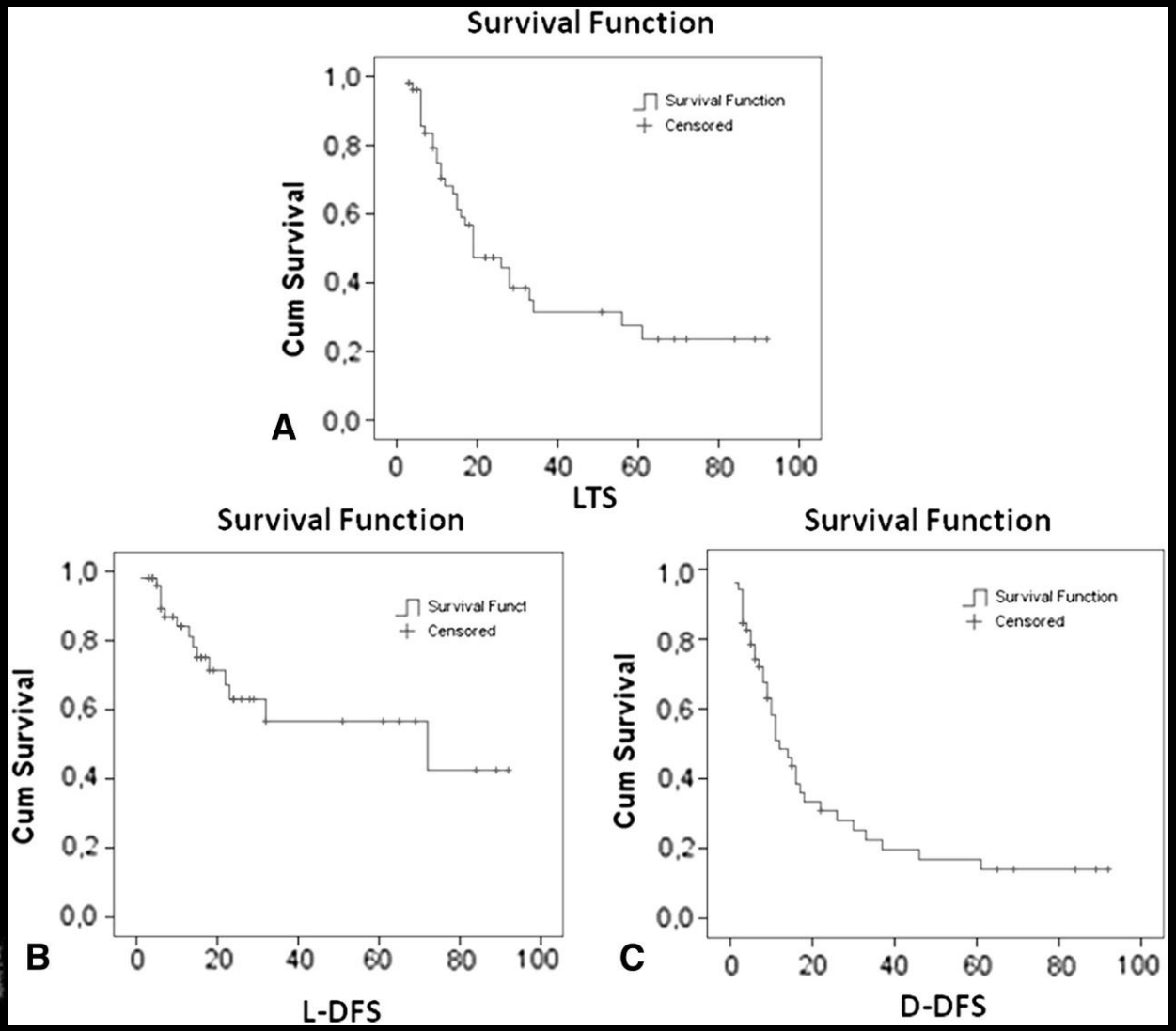


Journal of Thoracic Oncology 2012 7, 1547-1555DOI: (10.1097/JTO.0b013e318262caf6)

Surgery for oligometastatic non–small cell lung cancer: Long-term results from a single center experience

Maria Teresa Congedo, MD, Alfredo Cesario, MD, Filippo Lococo, MD, Chiara De Waure, MD, Giovanni Apolone, PhD, Elisa Meacci, MD, Sergio Cavuto, MD, Pierluigi Granone, PhD

The Journal of Thoracic and Cardiovascular Surgery 2012;144:444.



57 Patients
1997-2010

45 single metastasis

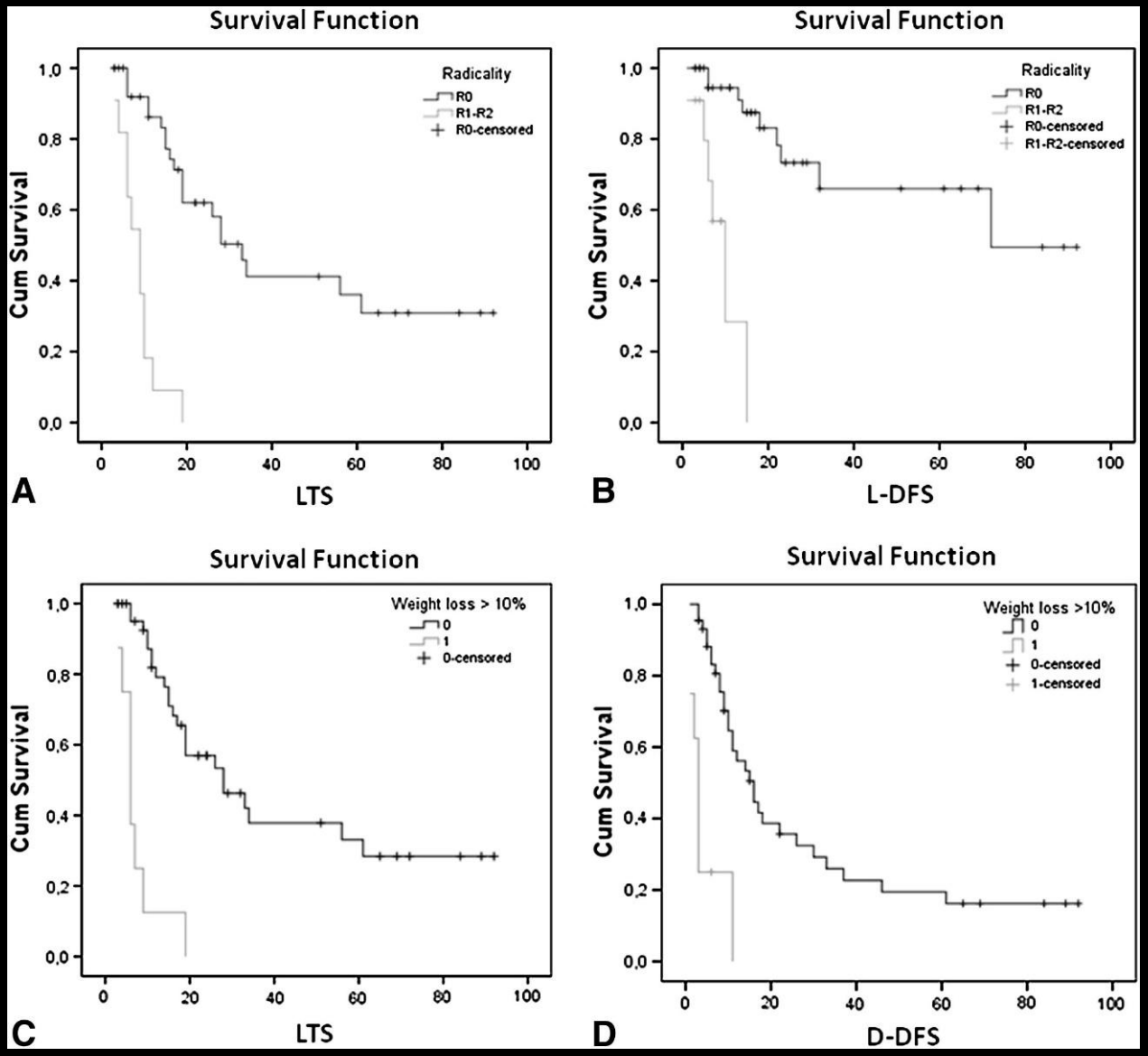
12 double metastasis

39 Brain

7 adrenal glands

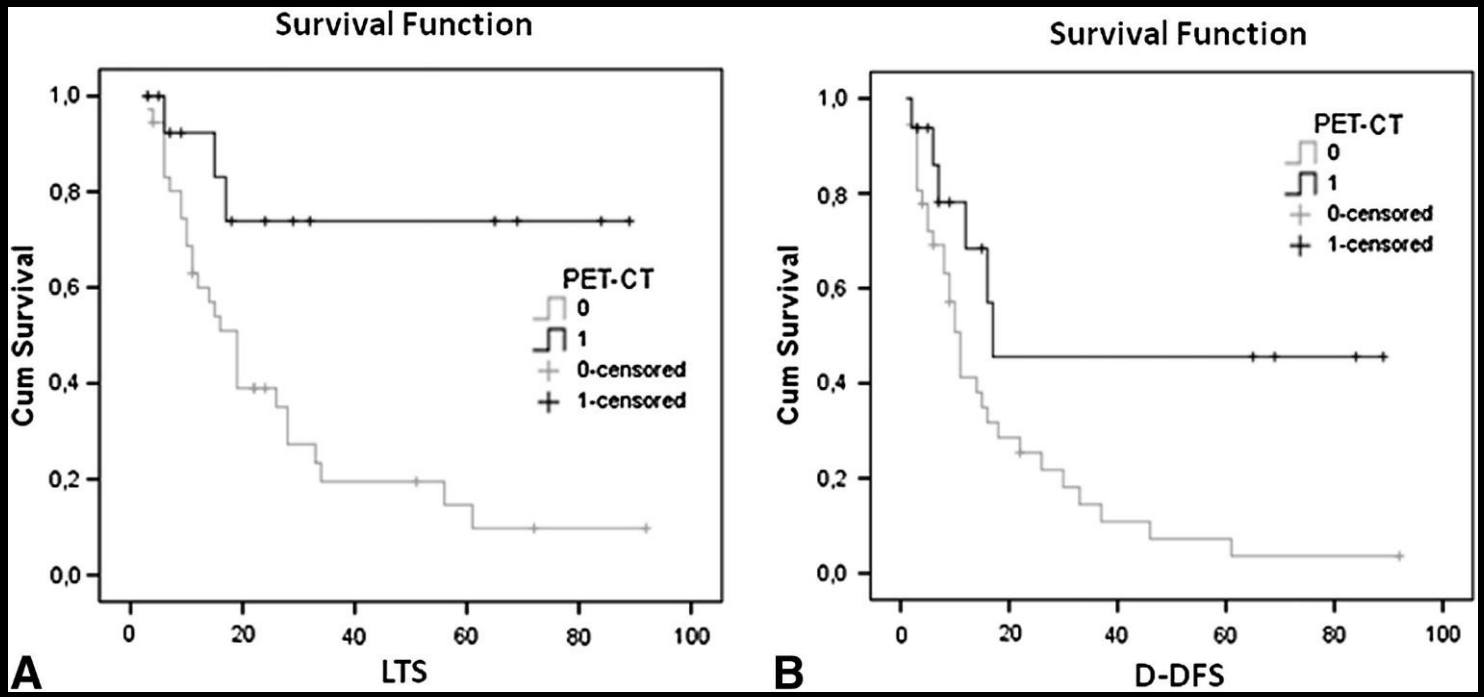
Surgery: n=42

Figure 2



The Journal of Thoracic and Cardiovascular Surgery 2012 144, 444-452DOI: (10.1016/j.jtcvs.2012.05.051)

Figure 4



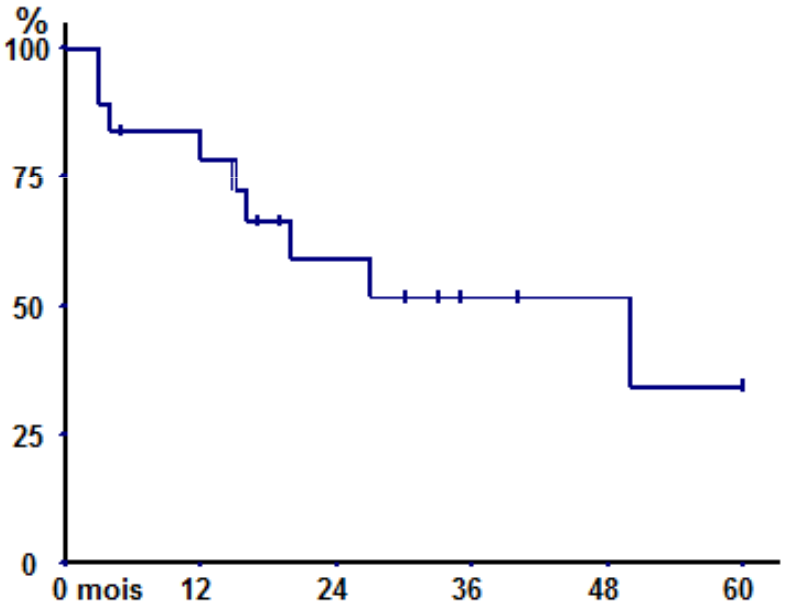
The Journal of Thoracic and Cardiovascular Surgery 2012 144, 444-452DOI: (10.1016/j.jtcvs.2012.05.051)

Adrenalectomy
HUPC experience
2001-2015
19 pts (0.2% of patients treated by lung resection)

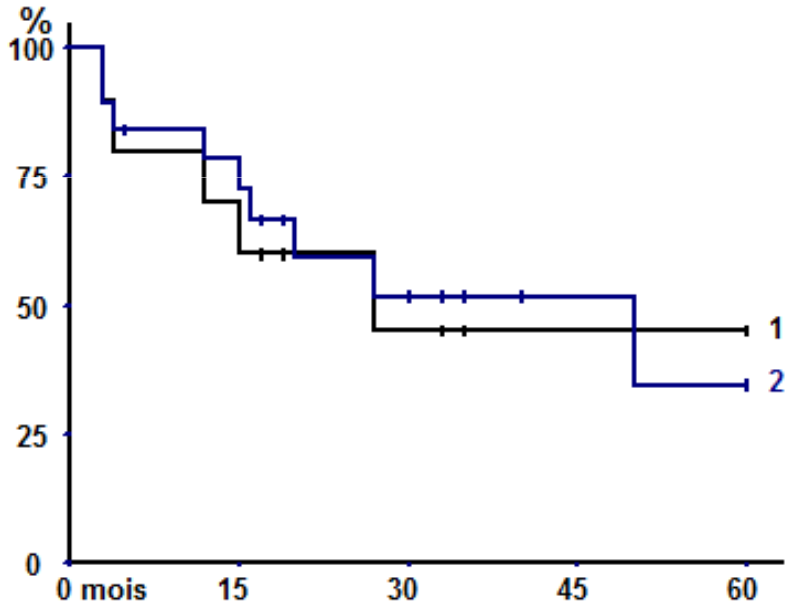
- 14 Men
- Median age 67 years; 66.7±10.0
- 17 previous lung resections; 1 exclusive Cht; 1 RT (brain)
    - 14 lobectomies
    - 1 bilobectomy
    - 2 pneumonectomies
- 18 pre-operative Cht; 1 postoperative Cht
- 15 ADK, 3 LARGE CELL, 1 NEUROENDOCRINE
- 5 T1, 9 T2, 5 T3
- 9 N0, 5 N1, 5 N2
    - 10 Synchronous
    - 9 Metachronous
        - DFI: 27.0±15.4 months ; Median 24 months

Adrenalectomy
HUPC experience
2001-2015
19 pts (0.2% of patients treated by lung resection)

- 9 Alives
- 8 dead



Synchronous (2) ves metachronous (1)



Conclusion

- Treatment of oligometastasic NSCLC have several **weeks points**:
  - A lack of clarity **as to the objectives**:
    - Definitive cure VS Prolonging survival
    - Local disease control VS Prevention of complication
    - Treatment of symptoms Vs palliation
  - **The rationale** for removal of metastases is insecure:
    - Radical local resection in a systemic disease is **"Oxymoron"**
    - Surgical Resection and Radiation Therapy could promote immune recovery of the disease
      - **Abscopal Effects of radiotherapy**
      - **Restoring immunosurveillance after surgery**
  - The evidence available does not address the question of whether **benefit exceeds harm**.

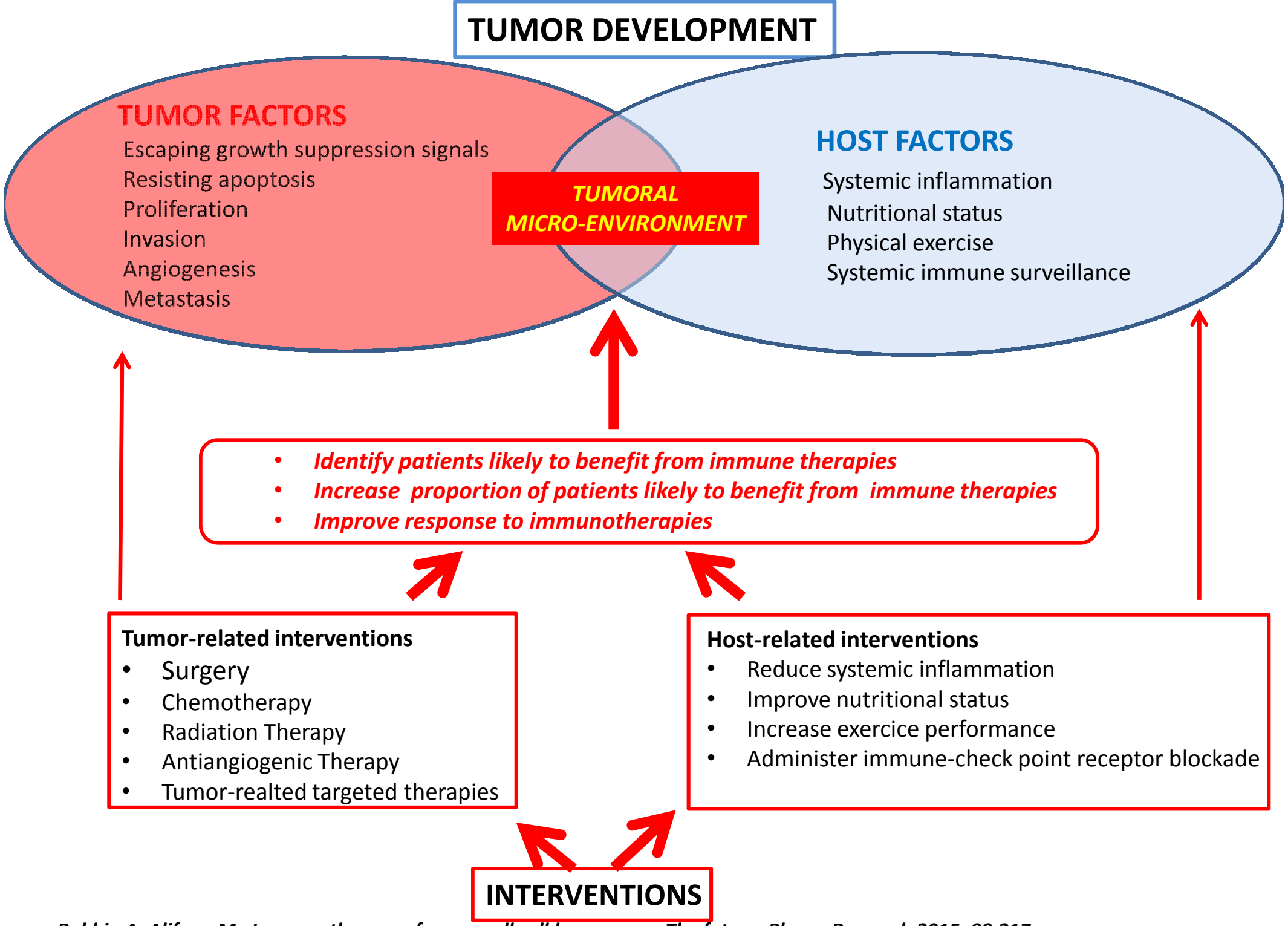
Conclusion

- The studies published are:
  - Observational almost always retrospective
  - Small cohorts
  - Collected over a long period of time
  - Absence of the control group

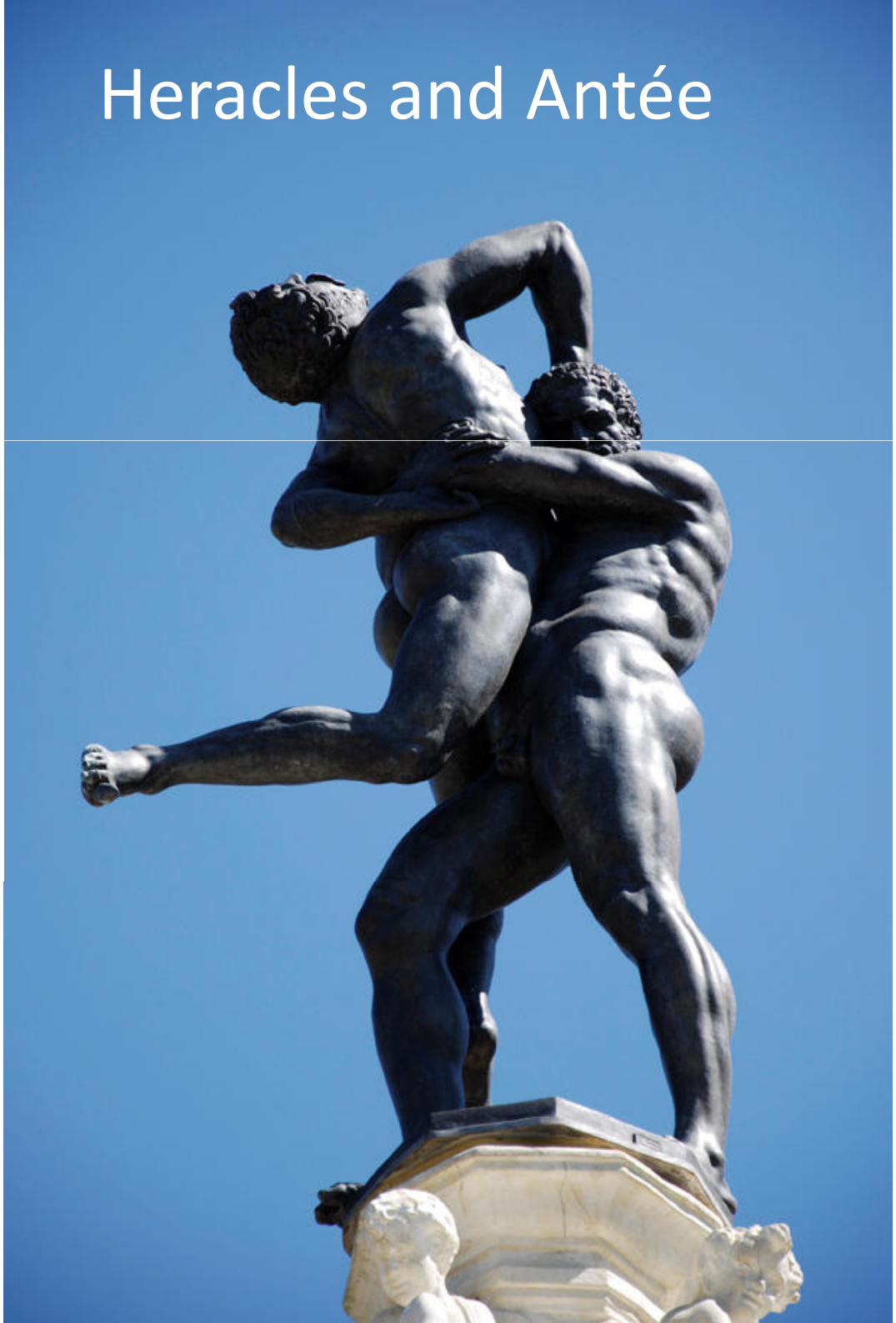
- Two randomized phase II trials recently initiated has been closed for slow accrual

There is a lacks of several crucial factors necessary for the tenets of

Evidence Based Medicine



Bobbio A, Alifano M. Immune therapy of non-small cell lung cancer. The future. Pharm Research 2015; 99:217



Oligometastic state is a clinical-radiological condition with a biological substrate not completely elucidated.

The better understand of prognostic factors ahead of stage (clinical anatomical disease) will help to define the possible role of local treatment for the cure of a systemic disease.