

# Tratamiento quirúrgico NSCLC, M1

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### NSCLC , M1 SINCRÓNICO

- Enfermedad metastásica
- **Metástasis cerebrales**
- Metástasis suprarrenales
- Nódulo/s pulmonares contralaterales
- Conclusiones
- Experiencia HU Miguel Servet

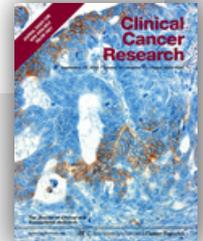
## **ENFERMEDAD METASTÁSICA**

- 30-40 % de pacientes con NSCLC al diagnóstico
- MSV 6-12 meses (2-4 meses si M1 cerebral)
- Localizaciones más frecuente: cerebro, hueso, hígado, glándula SR
- Metástasis “única” 10% de los NSCLC M1
- Estudios autópsicos....35% pac. tienen M1 cerebral
- Estudios autópsicos.... 25-40% de M1 cerebrales son “únicas”

## The Expression of Three Genes in Primary Non – Small Cell Lung Cancer Is Associated with Metastatic Spread to the Brain

Helena Grinberg-Rashi,<sup>1,8</sup> Efrat Ofek,<sup>2,8</sup> Marina Perelman,<sup>2,8</sup> Jozef Skarda,<sup>9</sup> Pnina Yaron,<sup>3</sup>

Clin Cancer Res 2009;15(5)

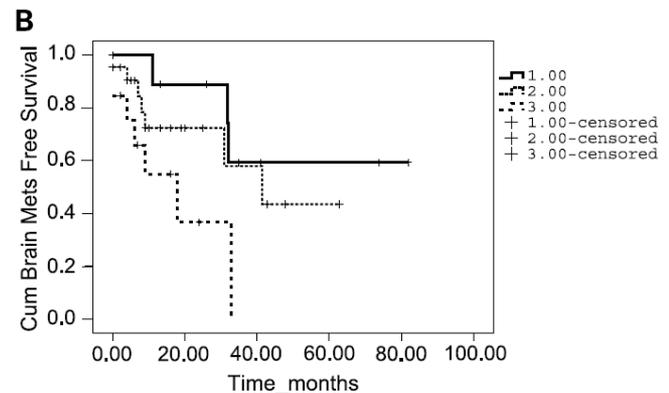
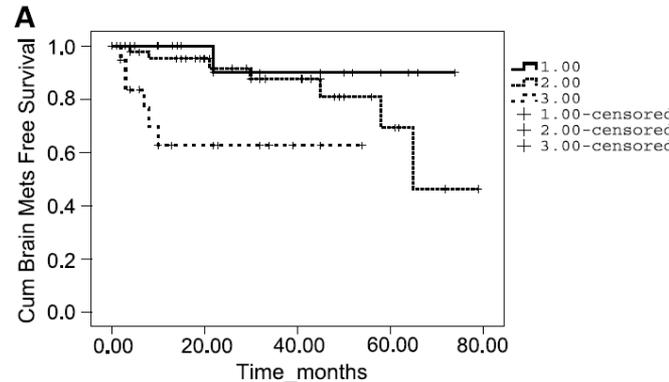


**Purpose:** Brain metastases from non-small cell lung cancer (NSCLC). We hypothesized that the expression of three genes could predict brain metastasis and be used for prognostic stratification and therapy.

**Experimental Design:** We performed a retrospective analysis of reverse transcriptase PCR (RT-PCR) data from a cohort of 100 NSCLC patients. A Cox regression analysis was used to evaluate the occurrence of brain metastases. The findings were verified in an independent cohort of 100 patients.

**Results:** A score based on the expression of three genes (*FALZ*, *KIF1A*, and *KIF1B*) was highly predictive of remaining brain metastasis-free survival in stage I/stage II tumors at 24 months (89% for patients with a low score vs 63% for patients with a high score,  $P < 0.01$ ). In patients with stage III/IV tumors, the 24-month brain metastasis-free survival was 89% for patients with a low score ( $P < 0.02$ ). These results were confirmed in an independent cohort of 100 patients.

**Conclusions:** The expression of three genes can identify patients at high risk of brain metastasis. The central nervous system (CNS) may be used to guide the central nervous system (CNS) in the treatment of NSCLC.



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# METÁSTASIS CEREBRALES



The NEW ENGLAND  
JOURNAL of MEDICINE

## A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

ROY A. PATCHELL, M.D., PHILLIP A. TIBBS, M.D., JOHN W. WALSH, M.D., ROBERT J. DEMPSEY, M.D.,

(N Engl J Med 1990; 322:494-500.)

M1 cerebral única (77% NSCLC), KPS > 70%  
54 pacientes

Excluidos 6p No Mtx en biopsia



Randomización



20%  
40 sem

Recidiva local  
MSV

52%  
15 sem

# METÁSTASIS CEREBRALES



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Año....2013

Craniotomía / SRT  
+ WBRT

*Paliativo*



Mejora SV

¿y el cirujano torácico?

*Selección de pacientes  
Estificación TN*



Tipo de resección

# ***METÁSTASIS CEREBRALES***

***...SERIES DE CASOS***



# METÁSTASIS CEREBRALES

J Thorac Cardiovasc Surg. 1976 Nov;72(5):690-8.

## **Pulmonary neoplasm with solitary cerebral metastasis. Results of combined excision.**

Magilligan DJ Jr, Rogers JS, Knighton RS, Davila JC.

### **Abstract**

Twenty-two patients underwent excision of a primary pulmonary neoplasm and solitary cerebral metastasis. Six patients had metastatic tumor removed on two occasions and there was one operative death in 28 craniotomies. Seven of 22 patients (32 per cent) survived one year following craniotomy and were free of significant symptoms for one year. Survival for at least 9 months and freedom from significant symptoms was achieved in a total of 12 patients (55 per cent). Relief of severe neurologic symptoms for a minimum of 3 months was achieved in 17 patients (77 per cent). The over-all one-year survival rate was 45 per cent and the average survival period is 14 months with 3 patients still living. The following factors had a favorable bearing on the outcome: Stage 1 lung cancer at pulmonary resection, whole-brain radiation therapy, and a longer interval between pulmonary resection and cerebral metastasis. The experience encourages us to pursue an aggressive surgical approach to pulmonary neoplasm and solitary cerebral metastasis.

PMID: 979310 [PubMed - indexed for MEDLINE]

- **1976. Magilligan (grupos de Detroit y Los Angeles)**
- **1ª gran serie específica de NSCLC. Mortalidad postop de la mtx cerebral muy baja (4%)**
- **22 p. Cirugía del tumor primario y mtx única (tanto sincronicos como metacronicos)**
- **Control de síntomas. SV (1 año) 45% y MSV 14m.**
- **Factores pronosticos favorables: NSCLC stadio I, adyuvancia WBRT, si metacronicos largo ILE**

# **METÁSTASIS CEREBRALES**

J Thorac Cardiovasc Surg. 1996 Jul;112(1):146-53.

## **Resection of single brain metastasis in non-small-cell lung cancer: prognostic factors.**

Mussi A, Pistolesi M, Lucchi M, Janni A, Chella A, Parenti G, Rossi G, Angeletti CA.

Servizio di Chirurgia Toracica, Dipartimento di Chirurgia, Università di Pisa, Italy.

- **52 pac. Cirugía combinada NSCLC y mtx cerebral unica**
- **Sincrónicos (19) vs metacrónicos (33)**
- **Remisión clínica neurológica 90%**
- **SV (5) 16%**
- **Factores favorables: N0, lobectomía, metacrónicos, ILE > 14 m.**
- **SV (5) 61% en pac N0 y metacrónicos (ILE>14m)**

# ***METÁSTASIS CEREBRALES***

J Thorac Cardiovasc Surg. 2001 Sep;122(3):548-53.

## **Surgical treatment of primary lung cancer with synchronous brain metastases.**

Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC.

Division of General Thoracic Surgery, Mayo Clinic and Foundation, Rochester, Minn 55905, USA.

- Sólo sincrónicos.
- 28 sincrónicos/220 pacientes sometidos a cirugía de mtx cerebrales de NSCLC
- SV (2) 54% (5) 21%.
- Factores adversos: N1-2

# ***METÁSTASIS CEREBRALES***

***....COHORTES RETROSPECTIVOS  
(paciente con y sin cirugía del tumor primario)***

# ***METÁSTASIS CEREBRALES***

J Neurosurg. 1995 Oct;83(4):605-16.

**Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991.**

Wroński M, Arbit E, Burt M, Galicich JH.

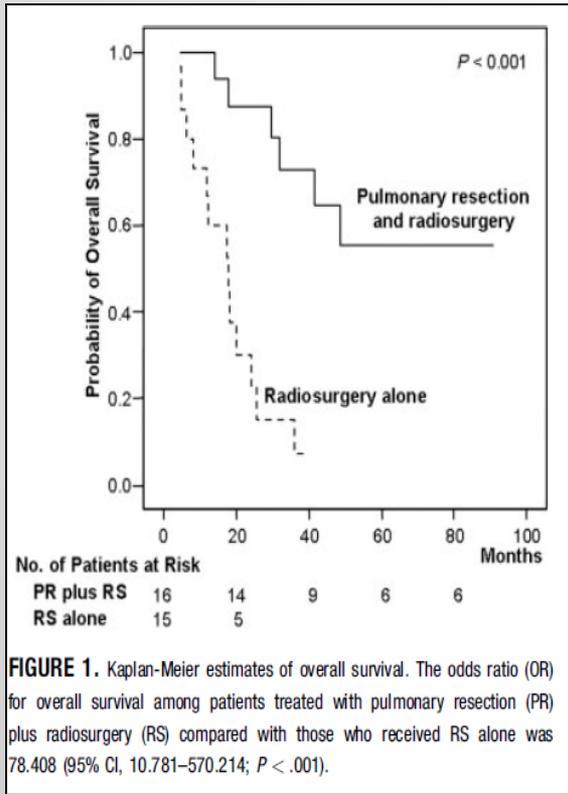
Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

- **231 pac sometidos a cirugía mtx cerebrales (1-3 mtx) de NSCLC (1976-1991)**
- **185/231 cirugía pulmonar**
- **37% sincronicas al tumor primario. (<60 días entre los dx)**
- **Mortalidad postop <3%**
- **SV (2) 24% (5) 12% (10) 5%**
- **Factores adversos: >60 años, M1 cerebelosa, no cirugía del tumor primario, mtx extracerebrales**

# METÁSTASIS CEREBRALES

## Pulmonary Resection in Patients With Nonsmall-Cell Lung Cancer Treated With Gamma-Knife Radiosurgery for Synchronous Brain Metastases

Cancer 2008



- KPS > 70. 1-3 Mtx cerebrales sincrónicas. Stage I-II NSCLC.
- Reseccion pulmonar + SRT cerebral (16p) vs SRT cerebral (15p)
- MSV 65 vs 18 meses ( $p < 0,001$ )
- Si resección pulmonar....SV (2) 87% (5) 56%
- Analisis multivariantede: Resección pulmonar: OR 78 (IC95% 10-570), QT: OR 5 (0,8-32)
- Durante el seguimiento, en el grupo de pacientes con cirugía pulmonar: menor incidencia de metástasis extracerebrales y menor recidiva cerebral “a distancia”
- Conclusion/hipotesis: el control local del tumor primario conlleva control de la enfermedad sistémica.

# METÁSTASIS CEREBRALES

[Int J Radiat Oncol Biol Phys.](#) 2008 Sep 1;72(1):19-23. doi: 10.1016/j.ijrobp.2007.12.031. Epub 2008 Feb 14.

## Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery.

[Flannery TW](#), [Suntharalingam M](#), [Regine WF](#), [Chin LS](#), [Krasna MJ](#), [Shehata MK](#), [Edelman MJ](#), [Kremer M](#), [Patchell RA](#), [Kwok Y](#).

Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD 21201, USA.

- 42 pac NSCLC (Estadio I-III) con M1 cerebral única tratada con SRT.
- Tratamiento radical del primario (26/42) (9 QRT, 12 Cirugía, 5 QRT + cirugía): MSV 26 m SV (5) 34%
- No tto radical del primario (16/42) MSV 13 meses SV (5) 0%
- Analisis multivariante significativos KPS y tratamiento radical torácico.

# METÁSTASIS CEREBRALES



TABLE 2. Surgical results of combined management for synchronous solitary brain metastasis and primary lung cancer<sup>1,11,12,16-19</sup>

Author	Year	No.	Therapy for brain metastasis	5-Year survival (%)	Median survival (months)	Poor prognostic factors
Torre et al <sup>16</sup>	1988	27	Craniotomy	15	26	Lymph node metastasis
Burt et al <sup>17</sup>	1992	65	Craniotomy	16	21	Incomplete resection
Billing et al <sup>1</sup>	2001	28*	Craniotomy	21	24	Lymph node metastasis
Bonnette et al <sup>18</sup>	2001	103 <sup>†</sup>	Craniotomy	11	12.4	Non-adenocarcinoma
Granone et al <sup>19</sup>	2001	20	Craniotomy	-	23	Non-adenocarcinoma and lymph node metastasis
Flannery et al <sup>12</sup>	2008	26 <sup>‡</sup>	SRS <sup>§</sup>	35	26.4	Karnofsky performance status
Yang et al <sup>11</sup>	2008	16	SRS	56	64.9	-
Current study	2008	17	Craniotomy and SRS	27	52	-

Interactive CardioVascular and Thoracic Surgery 8 (2009) 467-473

www.icvts.org

Best evidence topic - Thoracic oncologic

### Does surgery for primary non-small cell lung cancer and cerebral metastasis have any impact on survival?

Amit Modi, Hunaid A. Vohra, David F. Weedon\*

*Department of Thoracic Surgery, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK*

11/153 artículos seleccionados

The presence of any intra-thoracic lymph node involvement ( $N_1$  or  $N_2$ ) significantly affects 5-year survival adversely. We conclude that in the absence of mediastinal lymph node involvement, surgical resection of NSCLC with complete resection of the brain metastases improves prognosis with a median survival from 10 months to approximately 23 months. Furthermore, adenocarcinoma subtype, low CEA levels at presentation, positive response to induction chemotherapy and a high KPS have a positive prognostic value.

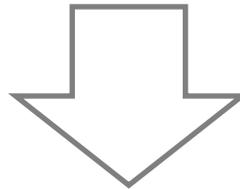
# METÁSTASIS CEREBRALES

**Pacientes con metástasis cerebral única de NSCLC**

*KPS > 70*

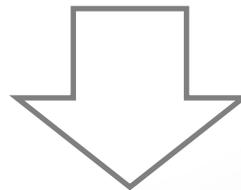
*No mtx extracerebrales*

Estadificación "N"



Tratamiento radical cerebral  
(Cirugía vs SRT) + WBRT

Estadificación "N"



Tratamiento radical tumor primario  
Cirugía mejor que QRT?

## Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation

Oscar Arrieta<sup>1,2,3\*</sup>, Cynthia Villarreal-Garza<sup>2</sup>, Jesús Zamora<sup>1,4</sup>, Mónica Blake-Cerda<sup>4</sup>, María D de la Mata<sup>1,4</sup>, Diego G Zavala<sup>2</sup>, Saé Muñoz-Hernández<sup>2</sup> and Jaime de la Garza<sup>1</sup>

*Radiation Oncology* 2011, **6**:166

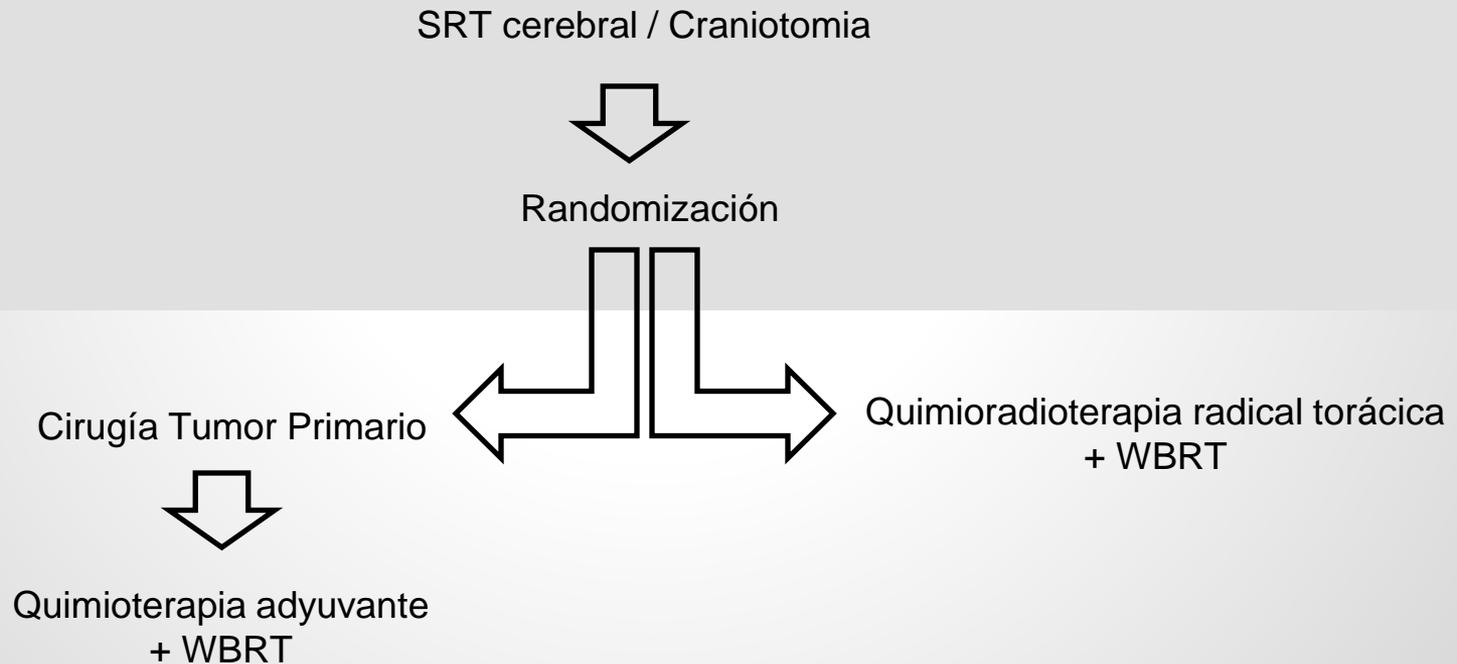
- **30 pac. M1 cerebral unica irresecable o multiple (no candidatos a craniotomia o SRT)**
- **WBRT.... QT (x2 ciclos) y si no progresion..... QRT (toracica)**
- **MSV 32m SV (2) 60%**
- **SV (3) N0-1... 60% SV (3) N2-3....24%**
- **SV tan elevadas puede ser debidas a sesgo de selección (solo incluyen pacientes que no progresaron despues de 2 ciclos de QT).**

*¿Por que ha de ser superior la cirugía a la QRT en el M1 solitario cuando no añade nada en el N2?  
(Albain. Intergroup 0139. Lancet 2009) (vanMeerbeek EORTC 08941. J Natl Can Inst 2007)*

# METÁSTASIS CEREBRALES

## “ESCENARIO IDEAL”

NSCLC (Tumor primario resecable) con M1  
*Criterios selección (T, N, KPS, otros...)*



# METÁSTASIS SUPRARRENALES

Nota clínica

## Tratamiento quirúrgico de la metástasis adrenal única en pacientes con cáncer de pulmón

Cristina Izquierdo-Vidal\*, Laureano Molins, Marc Boada, Esther Cladellas, Abel Gómez-Caro y Josep Maria Gimferrer

Servicio de Cirugía Torácica, Hospital Clínic, Barcelona, España

Med Clin (Barc). 2013;**140**(9):406–408

*Fundamento y objetivo:* El cáncer de pulmón (CP) puede afectar a la glándula adrenal como metástasis única. El objetivo de este estudio es describir la experiencia en nuestro centro sobre pacientes intervenidos quirúrgicamente de metástasis suprarrenal de CP en los últimos 11 años.

*Pacientes y método:* Se ha realizado un estudio retrospectivo descriptivo de los pacientes intervenidos quirúrgicamente de adrenalectomía por metástasis de CP.

*Resultados:* Se incluyen 7 pacientes con una mediana de edad de 64 años. A 5 de ellos se les realizó una lobectomía y a 2 una neumonectomía con tratamiento adyuvante según protocolo. La metástasis suprarrenal única se presentó de forma sincrónica en 3 pacientes y metacrónica en 4, entre 10 y 39 meses (mediana de 25 meses). Dos pacientes siguen vivos y con buena calidad de vida. La supervivencia media de los pacientes fue de 41 meses (intervalo de confianza del 95% [IC 95%] 7-74), y la supervivencia mediana, de 20 meses (IC 95% 7-32).

*Conclusiones:* Se puede afirmar que la cirugía de la metástasis adrenal por CP aumenta la esperanza de vida en determinados pacientes según la bibliografía disponible.

# METÁSTASIS SUPRARRENALES

J Surg Oncol. 1998 Sep;69(1):54-7.

## **Surgical management of adrenal metastases from lung cancer.**

Beitler AL, Urschel JD, Velagapudi SR, Takita H.

Department of Thoracic Surgical Oncology, Roswell Park Cancer Institute, Buffalo, New York 14263-0001, USA.

### **Abstract**

**BACKGROUND AND OBJECTIVES:** Adrenal metastases from lung cancer usually indicate systemic disease and incurability. However, a small subset of patients with isolated adrenal metastases may achieve long-term survival with aggressive surgical resection of the adrenal gland. To clarify the role of adrenalectomy for metastatic lung cancer, we undertook a review of the published literature on this topic.

**METHODS:** The English-language medical literature was searched for papers reporting surgical resection of adrenal metastases from lung cancer. Eleven articles were retrieved and their data pooled for analysis.

**RESULTS:** Sixty patients (including seven previously reported from our institution) formed the basis of this collective review. Thirty-two patients pooled from small series and case reports had a median survival of 24 months, and approximately one-third were 5-year survivors. Twenty-eight patients reported in two large series had a less favorable survival (approximately 14 months median survival).

**CONCLUSIONS:** Surgical resection of isolated adrenal metastases from lung cancer appears to have a modest survival advantage over nonoperative therapy, and it occasionally results in long-term survival. However, the relatively encouraging survival results reported in the literature could be related to careful patient selection for this aggressive therapy, publication bias in favor of positive treatment outcomes, or a combination of the two. Nevertheless, the results are encouraging enough to justify further investigation of this aggressive treatment strategy. Practical guidelines for management are proposed.

## NODULO/S PULMONARES CONTRALATERALES

### SÍNCRONICO vs M1b

Criterios de Martini y Melamed (1975)

IASLC “.... Los tumores múltiples de aspecto histológico similar deberían ser considerados como tumores **primarios sincrónicos solamente si**, en opinión del patólogo, y basándose en diferencias morfológicas, estudios inmunohistoquímicos y/o moleculares, representan **diferentes subtipos** del mismo tipo celular histológico o, en el caso de carcinoma escamosos, están asociados con un **carcinoma in situ**”

“....Sin metástasis ganglionares de mediastino ni en ganglios de drenaje en común”



CIRUGÍA



¿TIPO DE RESECCIÓN?

## ***NSCLC M1 sincrónico*** ***FACTORES PRONÓSTICOS FAVORABLES***

- Metástasis única
- Mtx supratentorial si cerebral
- Ausencia de afectación ganglionar torácica (N0)
- Tumores T1-2
- Tratamiento radical del tumor primario
- NO Neumonectomía
- Adenocarcinoma
- KPS > 80



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Non-Small Cell Lung Cancer



CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT

Stage IV, M1b: solitary site

- Pathologic mediastinal lymph node evaluation<sup>g</sup>
- Bronchoscopy
- Brain MRI
- PET/CT scan<sup>h</sup> (if not previously done)

Brain<sup>y</sup>

Adrenal

Pathologic diagnosis by needle or resection

Surgical resection, followed by whole brain RT (WBRT) (category 1) or stereotactic radiosurgery (SRS) or SRS + WBRT (category 1 for one metastasis) or SRS alone

Local therapy for adrenal lesion<sup>z</sup> (if lung lesion curable, based on T and N stage) (category 2B)<sup>aa</sup> or [See Systemic Therapy for Metastatic Disease \(NSCL-15\)](#)

T1-2, N0-1; T3, N0

T1-2, N2; T3, N1-2; Any T, N3; T4, Any N

Surgical resection of lung lesion<sup>k</sup> → Chemotherapy<sup>bb</sup> or Stereotactic ablative radiotherapy (SABR) of lung lesion or Chemotherapy<sup>bb</sup> → Surgical resection of lung lesion<sup>k</sup>

[See Systemic Therapy for Metastatic Disease \(NSCL-15\)](#)

Note: All recommendations are category 2A unless otherwise indicated.

## **CONCLUSIONES**

**Tratamiento radical M1 cerebral mejora control local y aumenta supervivencia**

**Tratamiento radical del primario y M1 única/oligomtx.... SV (2) 30-50% (5)10-30%**

**Cirugía pulmonar en casos muy seleccionados (*KPS, N, adenocarcinomas, lobectomía-cuña*)**

**Mayor evidencia, a pesar de peor pronóstico, que en la cirugía de mtx pulmonares**

**No existen RCT que confirmen el tratamiento radical más adecuado del tumor primario**

# ....*Nuestra Experiencia*

14 pacientes. M1 única cerebral

Tratamiento quirúrgico NSCLC y craniotomía (n=10) oSRT (n=4) cerebral

Neumonectomías (n=5) y N2 (n=4)

No mortalidad postoperatoria

MSV 16 meses

SV (5) 26%

