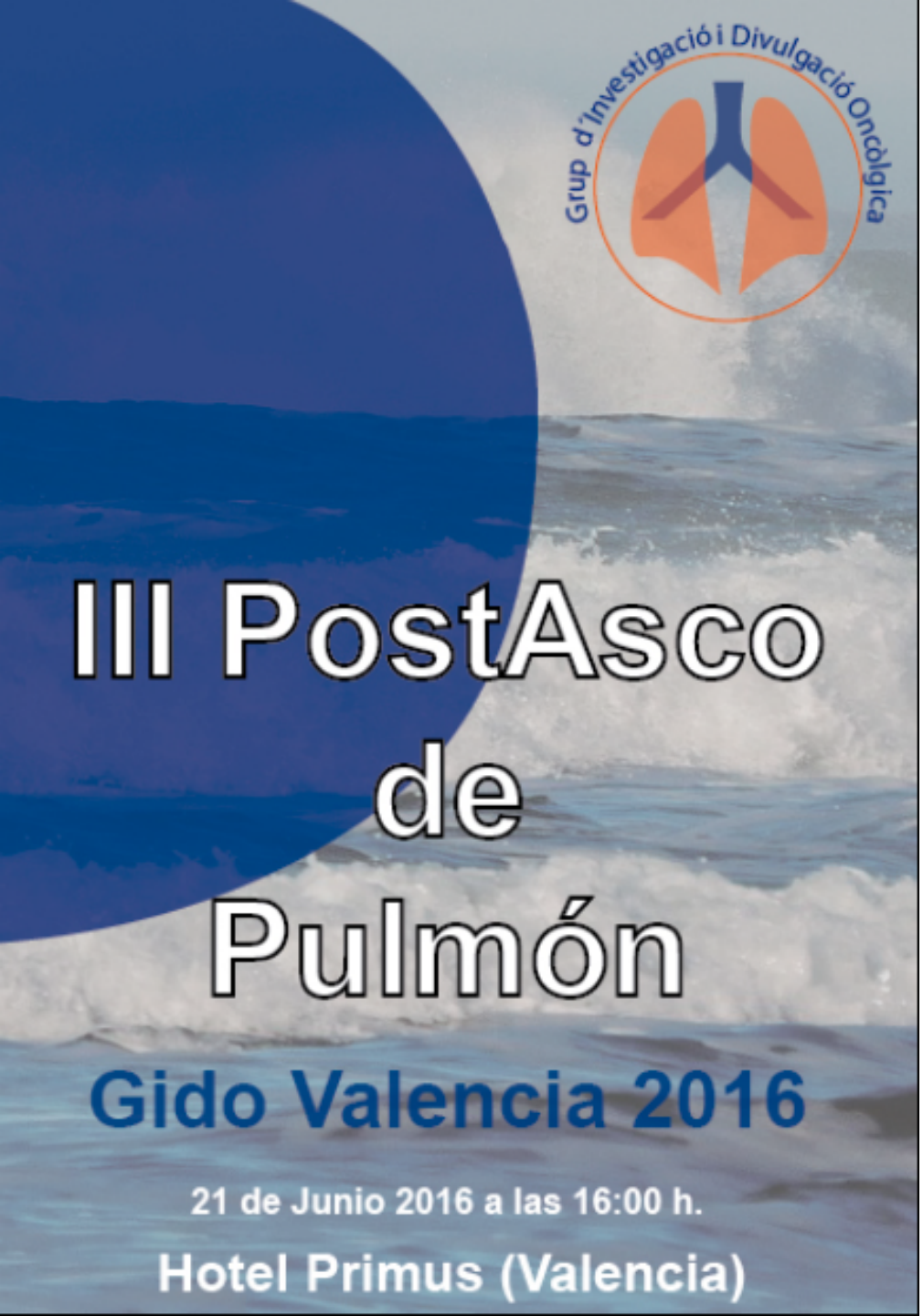


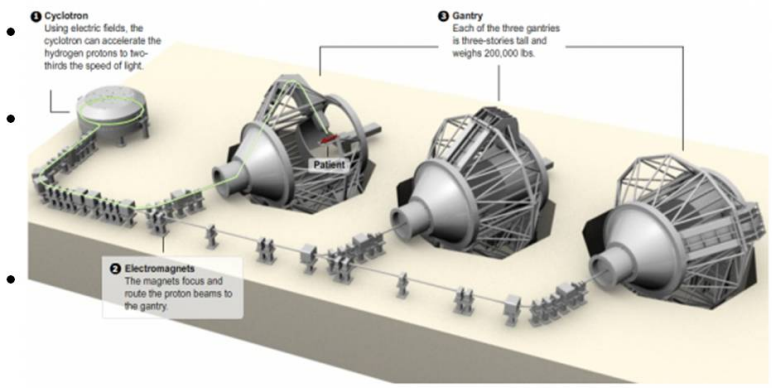

# Novedades en Radioterapia

L. Arribas Alpuente
Oncología Clínica
*(Antes Radioterápica)*

# Guión presentación

- Protones in lung cancer.
- Radioterapia del SCLC.
- Tratamiento local en enfermedad oligometastásica
- Tratamiento de metástasis cerebrales.
- Seguimiento interpretación de metástasis cerebrales.

# Promise of Proton Therapy in Lung Cancer?




## Considering the Role of Proton Therapy for Lung Cancer Patients

*Walter J Curran, Jr, MD*
*Executive Director*
*Winship Cancer Institute of Emory University*
*Atlanta, Georgia*

*NRG Oncology Group Chairman*

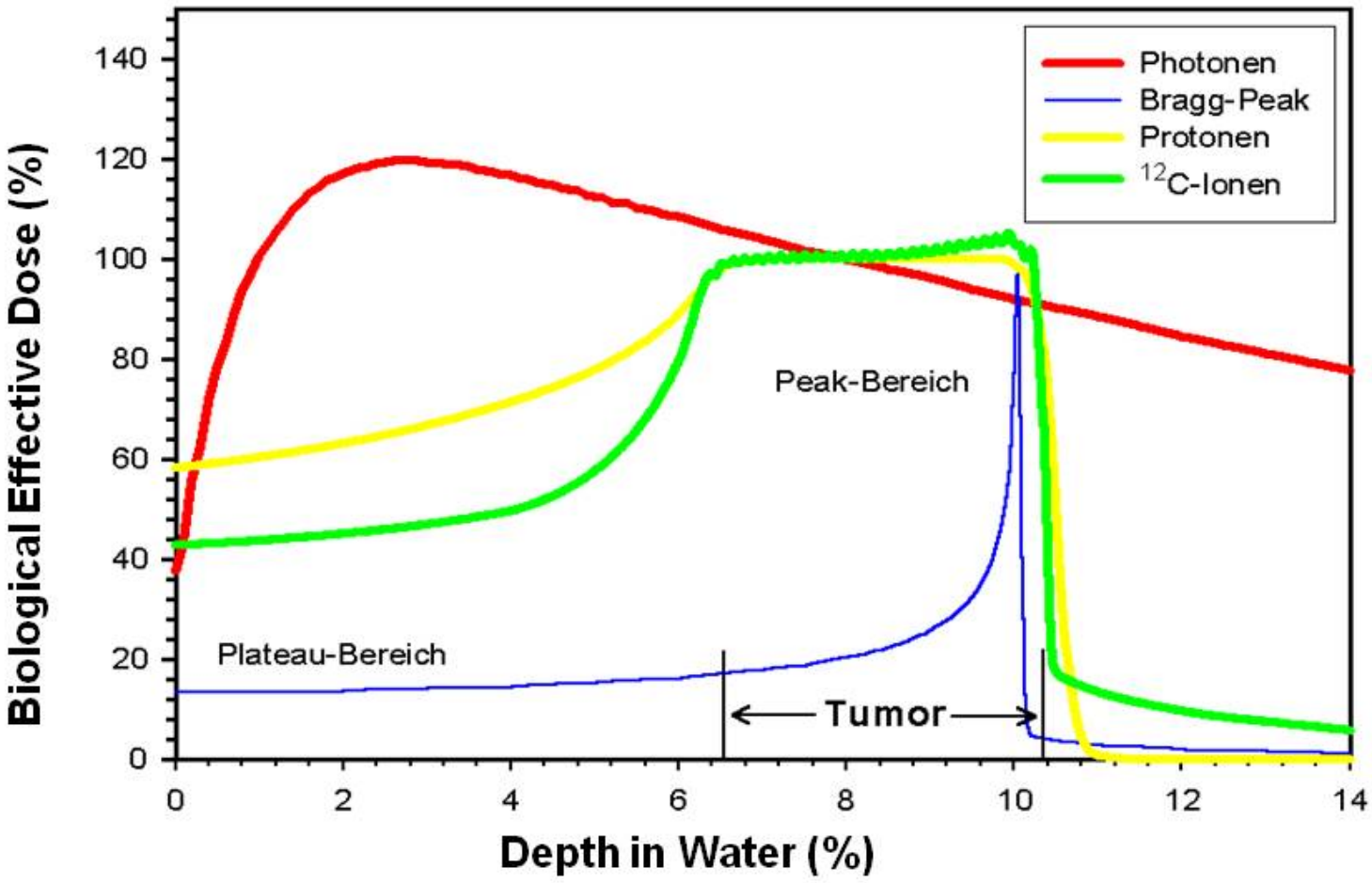
EMORY UNIVERSITY

## What Happens When Protons Meet Randomization

Maria Werner-Wasik, MD, FASTRO
Sidney Kimmel Cancer Center at Thomas Jefferson University
Philadelphia, PA, USA

PRESENTED AT: ASCO ANNUAL MEETING '16

# Protons and Ions Physical Dose Distribution

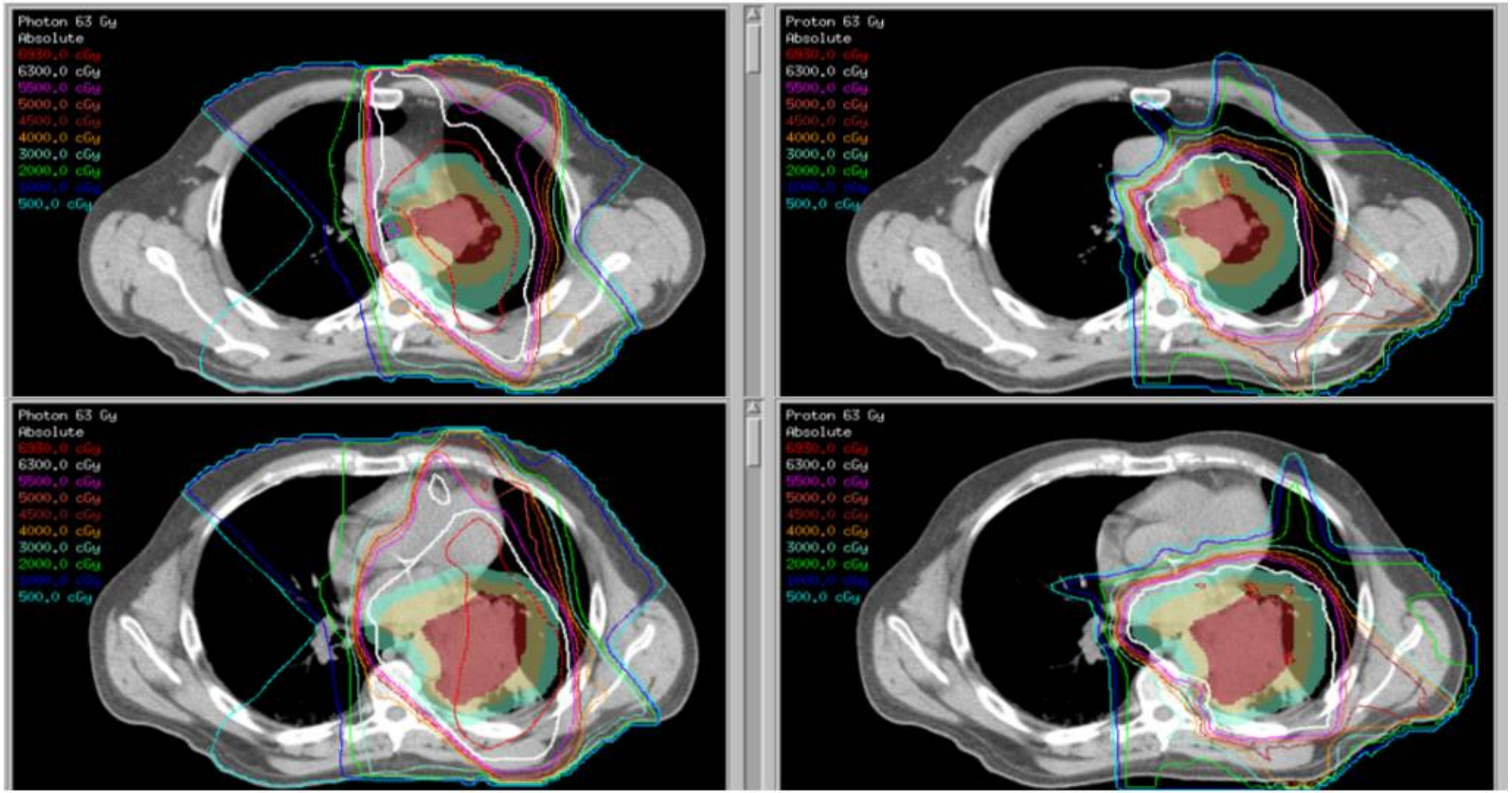



- Sparing of healthy tissue in the entry channel
- Steep dose fall-off behind the target / tumor

# 3D Radiation vs Proton for NSCLC

Photon 3D-CRT

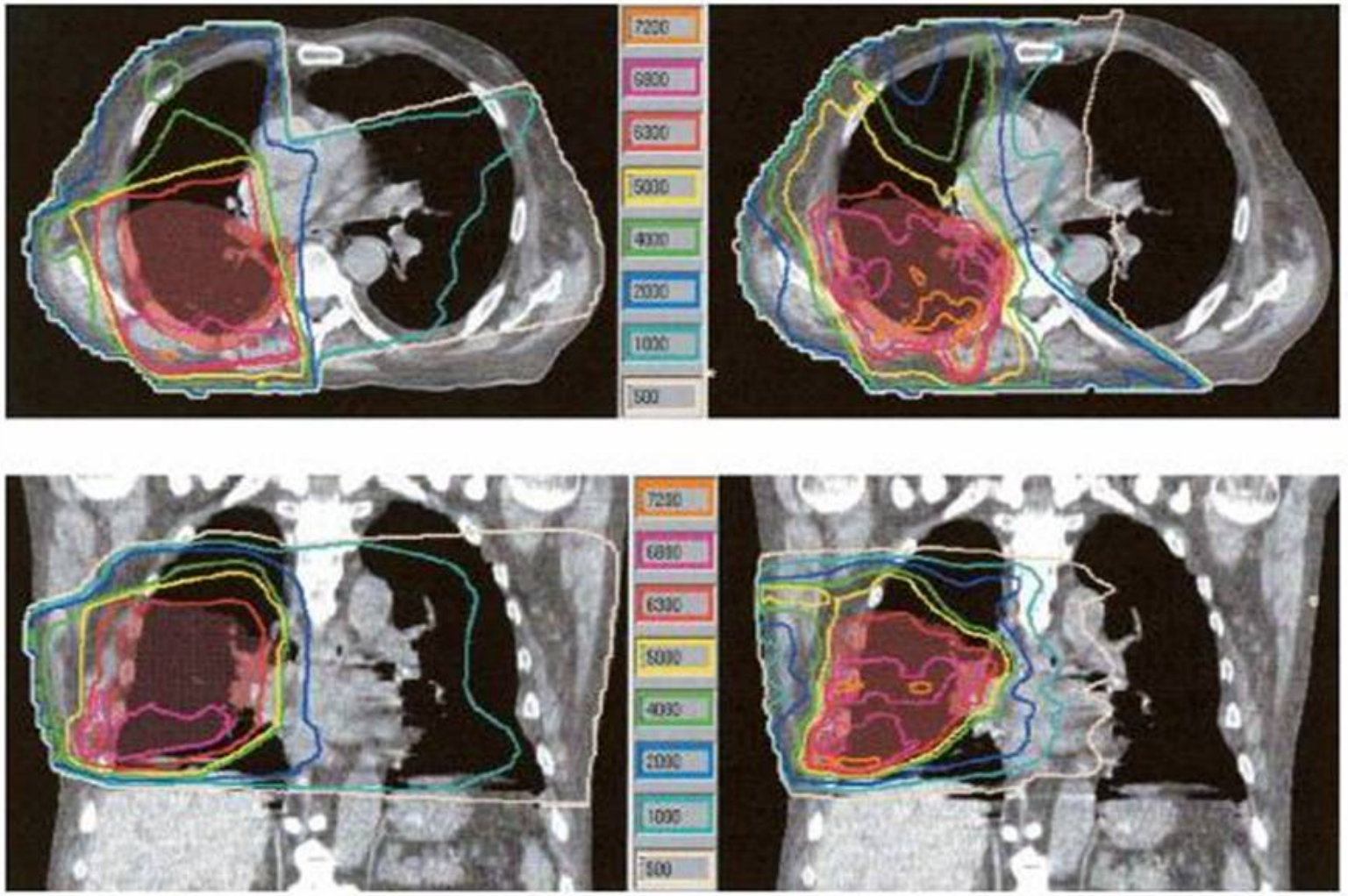
Proton




JOE Y. CHANG,
IJROBP Vol. 65, No. 4, pp. 1087–1096, 2006l

Presented By Walter Curran at 2015 ASCO Annual Meeting

# Improving Stage III Lung Ca Photon RT

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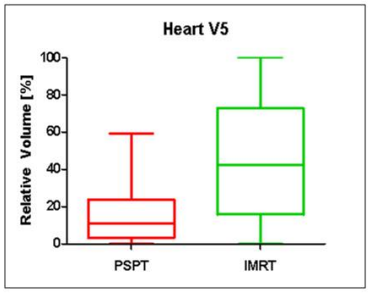
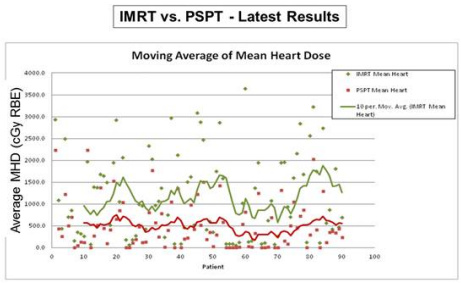
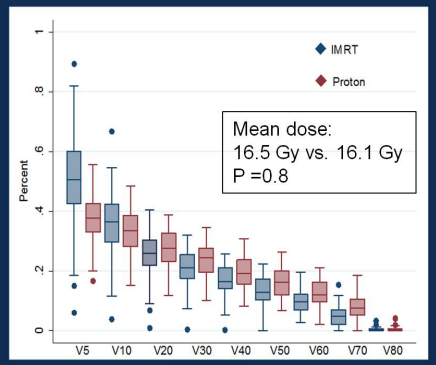
# Heart Dose: Protons vs IMRT

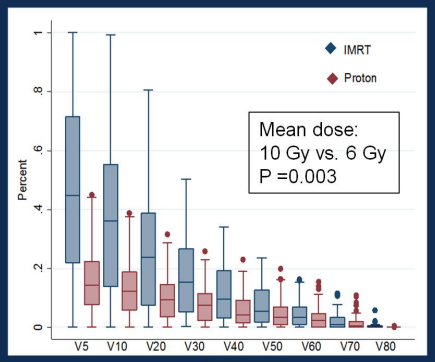



## Results: Mean Doses to Lung and Heart




Lung



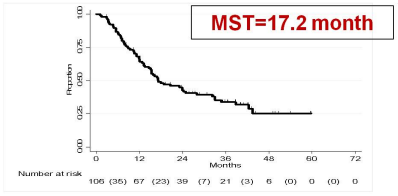

Heart

CO ANNUAL MEETING '16

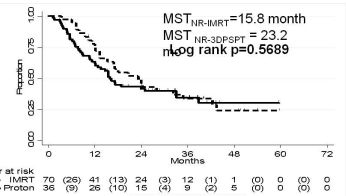
## Proton Therapy Associated with Better Survival

### OS in MDACC Trial: Non-Randomized Patients

Whole Group




NR-IMRT vs. NR-3D-PSPT




Cox Regression Analysis for NR OS

| Variable | HR | p-value | 0.95 | CI | Comparison Group |
|---|---|---|---|---|---|
| Ever smoking | 22.19 | 0.007 | 2.37 | 207.8 | Never |
| PTV | 1.01 | 0.016 | 1.00 | 1.02 | Continuous |
| Heart V5 | 4.27 | 0.03 | 1.15 | 15.90 | |

## MDACC Trial Results vs. RTOG 0617

- Local failure at 12 mo is lower than historic control (16-25% in 0617).
- Pneumonitis rate in photon arm is similar to the rate in 0617, but the proton arm's rate is higher than expected.
- Overall survival in the photon arm is essentially identical to the best arm of 0617, confirming it as the current survival benchmark.

PRESENTED AT: ASCO ANNUAL MEETING '16

Courtesy of Dr. James D. Cox, 2012

Presented By Walter Curran at 2015 ASCO Annual Meeting

# Protones: Resumen

- No hay evidencia, (ni la habrá, por la dificultad de realizar un ensayo aleatorizado al uso) del empleo de protones en el tratamiento del CP,
- Menor nº de neumonitis, menor dosis en corazón, con un control local similar (existen diferencias entre los 4 ensayos, con problemas de entrada de pacientes principalmente por las compañias aseguradoras).
- Es necesario un ensayo aleatorizado para responder a la pregunta….
- Tal vez en pacientes con EPOC severo con V20 pulmón por encima de 40 % o en pacientes cardiacos con lesiones en contacto con el corazón con riesgo de empeorar la patología cardiaca, los protones tengan alguna ventaja….para disminuir efectos secundarios .. Que ya es!!.

# Small Cell Lung Cancer and Radiotherapy

**Walter J Curran, Jr, MD**
**Executive Director**
**Winship Cancer Institute of Emory University**
**NRG Oncology Group Chair**

## Discussion Outline

Limited Stage SCLC

- Role of Thoracic RT
- Role of Prophylactic Cranial RT (PCI)

Extensive Stage SCLC

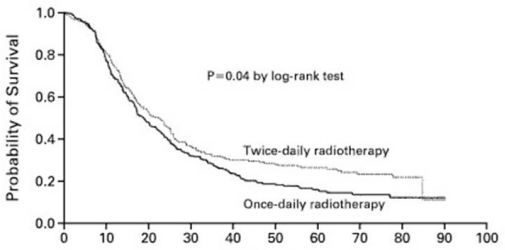
- Role of Consolidative Thoracic RT
- Role of PCI

No se puede mostrar la imagen en este momento.



# LD-SCLC: Concurrent Chemo-RT

- Accelerated hyperfractionated dose of 45 Gy twice daily (over 3 weeks) was better than 45 Gy in single daily fraction (over 5 weeks) in Intergroup 0096
- RTOG 97-12/ RTOG 02-39 showed feasibility of higher RT dose to 61.2 Gy (5 weeks given QD/BID)
- CALGB 39808 established the safety of 70 Gy QD




| Treatment Group | 0–20 Mo | 20–40 Mo | 40–60 Mo | 60–80 Mo | 80–100 Mo |
|---|---|---|---|---|---|
| | no. of deaths/no. at risk | | | | |
| Once daily | 108/206 | 48/96 | 15/47 | 4/21 | 0/5 |
| Twice daily | 100/211 | 47/109 | 7/62 | 5/42 | 1/14 |

# CONVERT Study Design

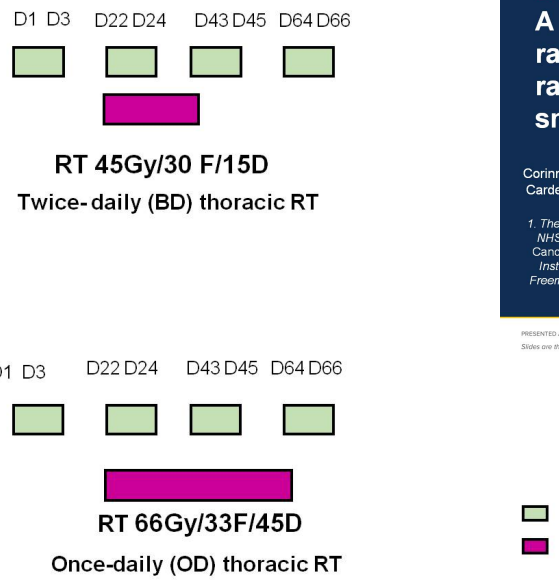
RTP after randomisation
RT started on D22 cycle 1
- 3DCRT or IMRT
- No ENI

QA programme

Chemotherapy
4 to 6 cycles
- Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1
- Etoposide 100mg/m2 D1-3

Stratification factors
- Centre
- Nb cycles chemo:4 vs.6
- PS: 0,1 vs. 2

Limited Stage Small Cell




Presented by: Prof C Faivre-Finn

## CONVERT trial

**Concurrent ONce-daily VErsus twice-daily RadioTherapy: A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited-stage small cell lung cancer and good performance status**


Corinne Faivre-Finn[1], Michael Snee[2], Linda Ashcroft[3], Wiebke Appel[4], Fabrice Barlesi[5], Adi Bhatnagar[6], Andrea Bezjak[7], Felipe Cardenal[8], Pierre Fournel[9], Susan Harden[10], Cecile Le Pechoux[11], Rhona McMenemin[12], Nazia Mohammed[13], Mary O'Brien[14], Jason Pantarotto[15], Veerle Surmont[16], Jan Van Meerbeeck[16], Penella Woll[17], Paul Lorigan[1], Fiona Blackhall[1]

*1. The University of Manchester, Institute of Cancer Sciences, Manchester, UK; 2. St James Hospital, Leeds, UK; 3. MAHSC-CTU, The Christie NHS Foundation Trust, UK; 4. Royal Preston Hospital, UK; 5. CHU de Marseille, France; 6.Southampton General Hospital, UK; 7.Canadian Cancer Trials Group, Princess Margaret Cancer Center, Toronto, Canada; 8. GECP, Institut Català d'Oncologia, Barcelona, Spain; 9. GFPC, Institut de Cancérologie de la Loire, France; 10. Addenbrookes Hospital, Cambridge, UK; 11. Institut Gustave Roussy, Villejuif, France; 12. Freeman Hospital, Newcastle-upon-Tyne, UK; 13. Beatson Cancer Centre, Glasgow, UK; 14. Royal Marsden Hospital, Surrey, UK; 15. Ottawa Health Research Institute, Canada; 16. Universiteit Gent, Belgium; 17. Weston Park Hospital, Sheffield, UK*



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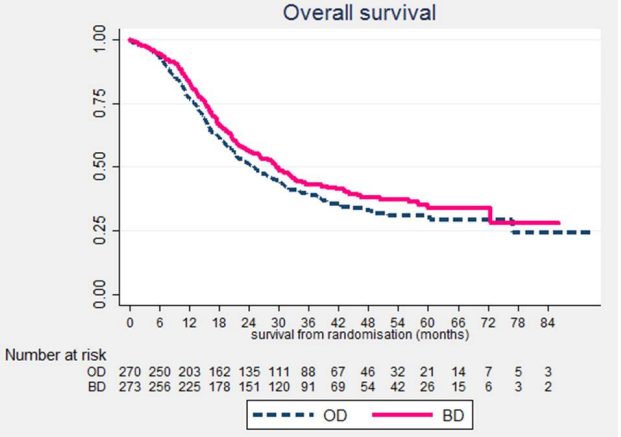
Presented by: Prof C Faivre-Finn @finn_corinne

# CONVERT: Overall Survival




**Primary objective-survival at 2-years**
**Expected survival BD arm 44%**
**Projected survival OD arm 56%**

**Median follow-up: 45 months**

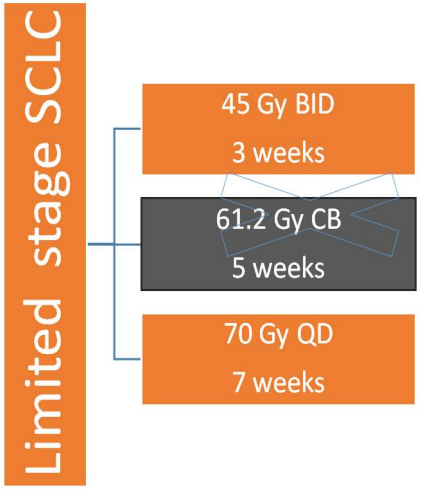
| Overall survival (n=543) | BD | OD | Log-rank |
|---|---|---|---|
| Median (months) | 30 (24-34) | 25 (21-31) | p=0.15 |
| 1-year | 83% (78-87) | 76% (71-81) | |
| 2-year | 56% (50-61) | 51% (45-57) | |
| 3-year | 43% (37-49) | 39% (33-45) | |

al Meeting

Presented by: Prof C Faivre-Finn

# CALGB30610/RTOG 0538 Ongoing Trial

- Will 70 Gy in single daily fractions offer superior clinical benefit over 45 Gy BID?




## Current Status in LD-SCLC
## RT Dose and Fractionation

- Lacking only a Phase III Equivalence Trial, there is support for using either 45 Gy in 1.5 Gy BID or 66 Gy in 2.0 Gy qD

- Selection of the best approach may relate to patient fitness and patient & medical care logistics

# LD-SCLC PCI

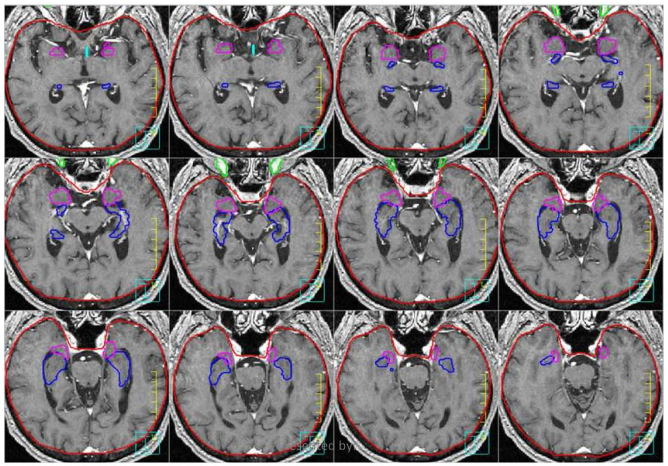
- Well Established in Meta-Analyses
- Survival Advantage Seen when delivered to LD-SCLC after CR to Chemo-RT
- Standard Regimen is 25 Gy in ten 2.5 Gy Fractions
- Alternative Regimens not Superior
- Neuro-Cognitive Effects Still a Concern

## Neurocognitive Effect Reduction

- RTOG phase III trial testing menantine among brain met patients
- Hippocampal sparing whole brain radiation therapy
- Identification of high vs low risk patients for in-brain relapse



## Hippocampal Volume Definition





ing

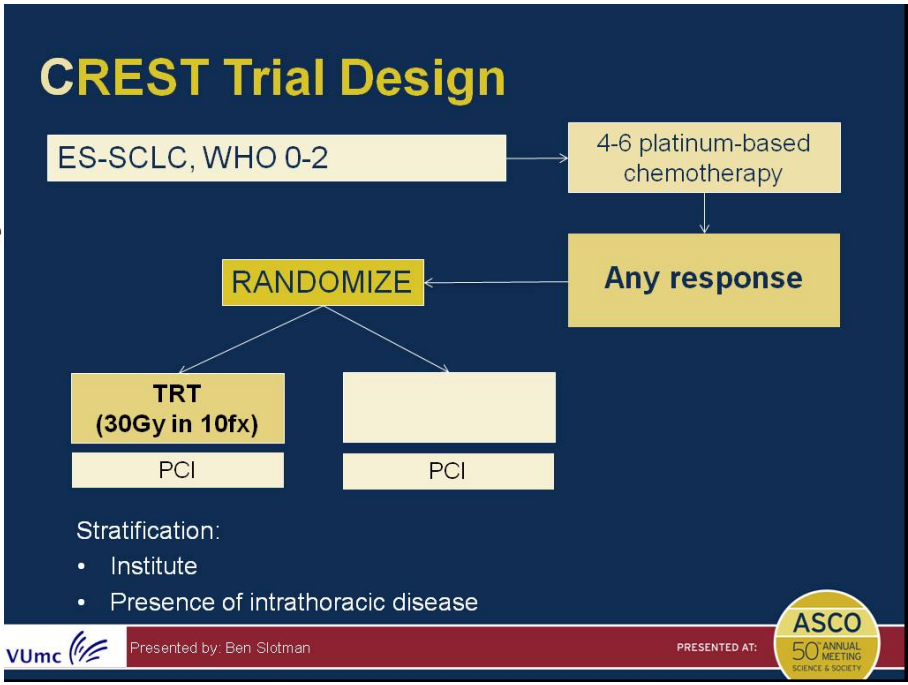
# Ya está en marcha un ensayo con RTH con protección del hipocampo

## NRG Oncology CC003
## A Randomized Phase II/III Trial of PCI with or without Hippocampal Avoidance (HA) for SCLC

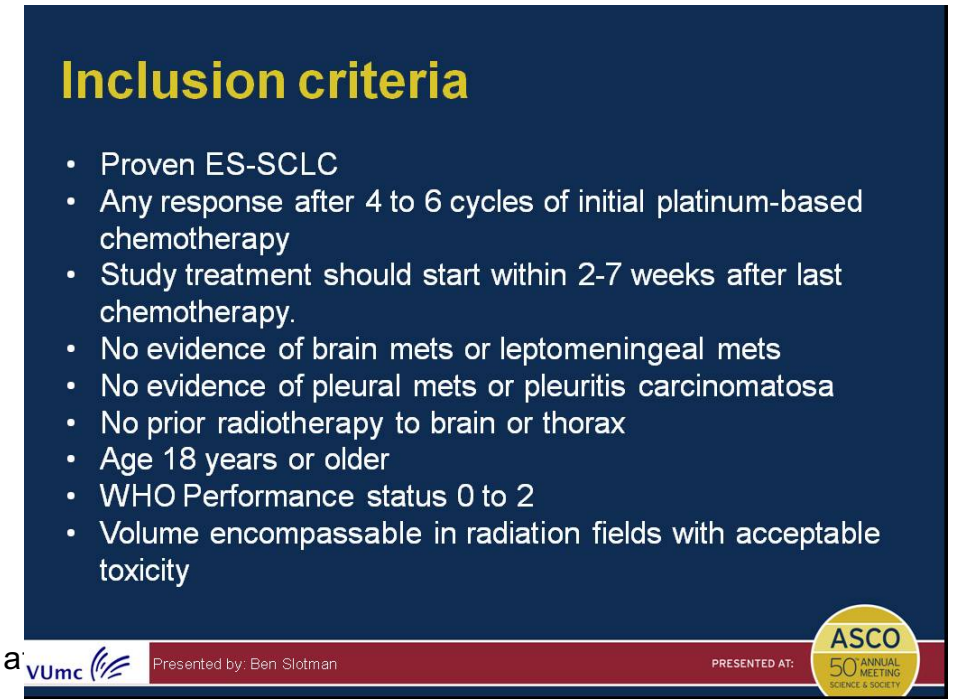
- Randomized Phase II Component (Non-Inferiority): Determine whether the 12-month intracranial relapse rate following HA-PCI is non-inferior compared to the rate following PCI for patients with SCLC
- Phase III Component (Efficacy): Determine whether HA-PCI reduces the likelihood of 6-month deterioration from baseline in HVLT-R delayed recall compared to PCI for patients with SCLC

## Consolidative Thoracic RT *for ED-SCLC Patients?*

- No historic role for thoracic RT after chemo response
- Should this be re-considered under the concept of "Oligometastatic" disease?
- The CREST trial (Slotman, et al Lancet 2015)

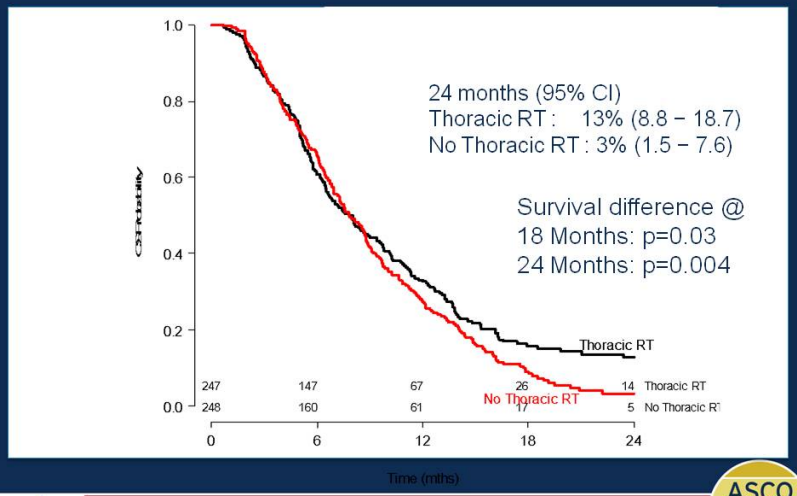







Presented By Walter Curran a

## Overall survival




VUmc Presented by: Ben Slotman PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

## CREST Trial (Lancet 2015)

| | TRT (n=247) | | Control (n=248) | |
|---|---|---|---|---|
| **Response** | | | | |
| Complete response | 12 | ( 4.9) | 13 | ( 5.2) |
| Partial response | 180 | (72.8) | 170 | (68.6) |
| "Good" response | 55 | (22.3) | 65 | (26.2) |
| **Persistent intrathor. disease** | | | | |
| Yes | 215 | (87.0) | 219 | (88.3) |
| No | 32 | (13.0) | 29 | (11.7) |

Presented by:

Survival +/- TRT

## CREST Trial Survival Results

- 2-Year Survival Rates by Arm Assignment (95% CI)
  - Thoracic RT : 13% ( 8.8 – 18.7 )
  - No Thoracic RT : 3% ( 1.5 – 7.6 )
- Survival difference @
  - 18 Months: p=0.03
  - 24 Months: p=0.004
- Survival @ 12 Mo was Primary Endpoint: NS

Presented by:

## Conclusions

Thoracic radiotherapy (30 Gy in 10 fx) in ES-SCLC

- Improves overall survival
- Improves progression-free survival
- Improves intrathoracic control

Thoracic radiotherapy should be offered in addition to PCI to all ES-SCLC patients responding to initial chemotherapy

VUmc Presented by: Ben Slotman PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Walter Curran at 2016 ASCO Annual Meeting

## CREST Trial Caveats

- Well-Executed, Adequately Powered Trial
- "Good" Response: Between PR and NR?
- 24% of Those Enrolled
- 88% of Enrolled Pts have Residual Thoracic Disease
- Was There Greater or Lesser Benefit than for True Responders?
- **Hazard Ratio Goal: 0.76**
- **Hazard Ratio Reached: 0.84 (p =0.066)**

Presented by:

# ED-SCLC PCI

- Not Established as Standard of Care following Chemotherapy
- EORTC Trial (Slotman et al NEJM 2007 ) Raised t
  Issue
- Conflicting Trial from Japan (Seto et al, ASCO 20

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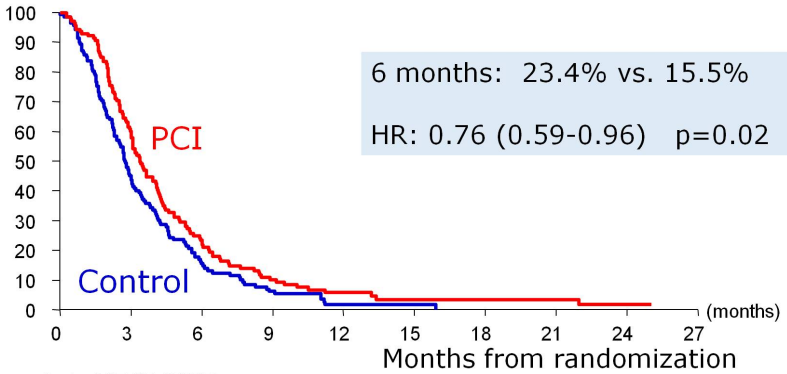
**Failure-free survival (EORTC 2007)**

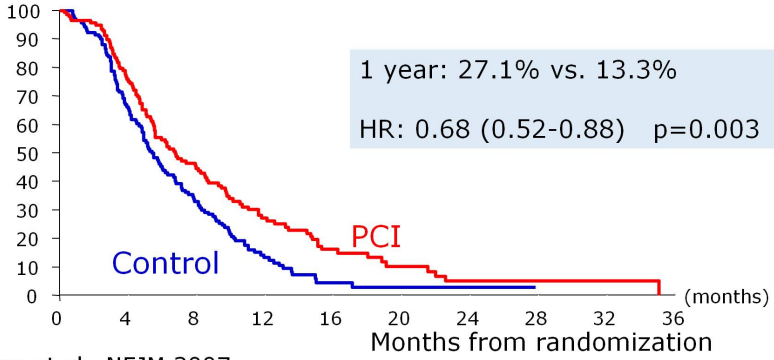



6 months: 23.4% vs. 15.5%

HR: 0.76 (0.59-0.96) p=0.02

Slotman et al.. NEJM 2007

**Overall Survival (EORTC 2007)**



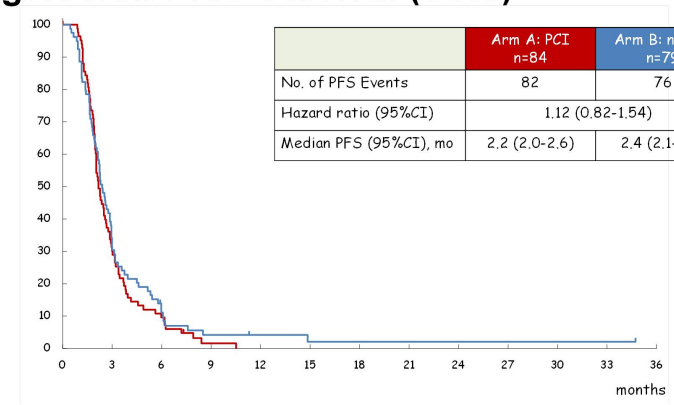

1 year: 27.1% vs. 13.3%

HR: 0.68 (0.52-0.88) p=0.003

Slotman et al.. NEJM 2007

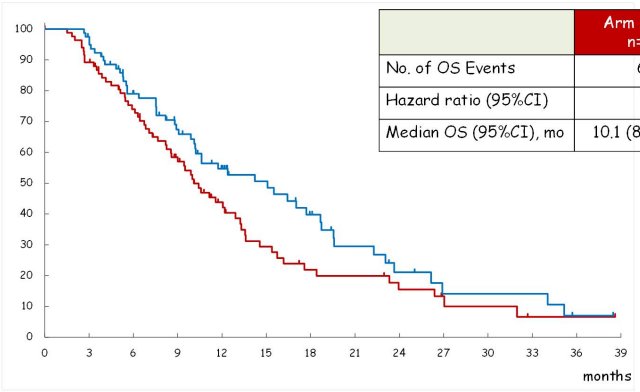
Presented By Walter Curran at 2016 ASCO Annual Meeting

## Progression-Free Survival (Seto)




| | Arm A: PCI n=84 | Arm B: no PCI n=79 |
|---|---|---|
| No. of PFS Events | 82 | 76 |
| Hazard ratio (95%CI) | 1.12 (0.82-1.54) | |
| Median PFS (95%CI), mo | 2.2 (2.0-2.6) | 2.4 (2.1-2.9) |

## Survival (Sato)




| | Arm A: PCI n=84 | Arm B: no PCI n=79 |
|---|---|---|
| No. of OS Events | 61 | 50 |
| Hazard ratio (95%CI) | 1.38 (0.95-2.02) | |
| Median OS (95%CI), mo | 10.1 (8.5-13.2) | 15.1 (10.2-18.7) |

Progre

# PCI for Extensive Stage SCLC

- **Japanese Trial Follows Standards of US Care in Terms of Neuro-Imaging and PCI Dose and Study Endpoints**
- **Positive Effect on Survival for EORTC Trial Still Difficult to Understand**
- **If Hippocampal Avoidance PCI is proven effective and with reduced risk of neurocognitive effects, the risk/benefit ratio for PCI in ED-SCLC may change.**

Presented by:

Presented By Walter Curran at 2016 ASCO Annual Meeting

# Small Cell: Para llevar a casa

- Enfermedad limitada:
  - RTQT concomitante con 1-2º ciclo sigue siendo el estándar.
  - Fraccionamiento: Los problemas de tratar dos veces al día a los pacientes no están justificados por un aumento en la OS.(CONVERT Trial)
  - La PCI en E. Limitada: Si, pendientes del ensayo con protección del Hipocampo, para disminuir los efectos deletéreos sobre la memoria.
- Enfermedad extendida:
  - La RT torácica mejora la supervivencia (CREST, Slotman ).
  - LA RT holocraneal (ICP) mejora la supervivencia, (Slotman 2007)continúan los problemas con el trabajo de Seto 2015.

# Local Therapy in the Form of Radiation for Stage IV NSCLC in the Consolidative, Oligoprogressive, or/and Abscopal Setting

Puneeth Iyengar, MD, PhD
Assistant Professor of Radiation Oncology
Leader of Thoracic Radiation Oncology Program
UT Southwestern Medical Center
Dallas, TX, USA



## Indications for Local Therapy

1) Consolidation

2) Oligoprogression

3) Abscopal Effects

ASCO 2016
UTSouthwestern Medical Center

## Rationale – Local Tx for Mets

Up to 70% of patients with stage IV NSCLC achieve either a partial response or stable disease to first line systemic therapy (Capuzzo et al)

Progression occurs within median of 3-4 months after last cycle.

In those patients who do show progression of disease, up to 64% progress only at sites present prior to the start of first line chemotherapy (Mehta et al, Rusthoven et al).

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## Limited Metastatic Disease

Support for the benefit provided by treatment of limited metastases was first derived from surgical metastectomy.

Patients treated with surgical resection of hepatic, pulmonary, or adrenal metastases have had improved rates of survival with resection for sarcoma and colorectal cancer (Fong et al, Pastorino et al, Miller et al, Strong, V. E. *et al*).

Adrenalectomy in patients with metastatic NSCLC with 5 year OS of 25% (Tanvetyanon et al)

Resection of brain metastases in patients with metastatic NSCLC with 5 year OS of 13% (Wronski et al)

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## Stereotactic Body Radiation Therapy

### Benefits

Non invasive

No surgical side effects/post op recovery

Anatomical sites more amenable SBRT beams



## SBRT FOR LMD – All Primaries

| Radiation series Site | Year | Patients | Survival,% |
|---|---|---|---|
| Hoyer et al. (CRC) Lung, liver, adrenal | 2006 | 64 | 38-13 |
| Hof et al Lung | 2007 | 61 | 47.8 |
| Kutz et al. Liver | 2007 | 69 | 24 |
| Rusthoven et al. Liver | 2009 | 47 | 30 |
| Rusthoven et al. Lung | 2009 | 38 | 39 |
| Lee et al. Liver | 2009 | 70 | 47 |
| Kang et al. (CRC) Multiple | 2010 | 59 | 39 |

SI

## Treatment in Stage IV NSCLC

How do we treat stage IV NSCLC patients after 1st line systemic therapy if they have had partial response/stable disease and limited sites of gross residual disease?

Current paradigm:

- Maintenance chemotherapy
- Observation with initiation of 2nd line therapy at time of progression

Proposed paradigm:

- Locally treatment with SBRT as part of 1st line/maintenance therapy



## Limited Metastatic Disease

Data Suggest:

Patients with limited sites of metastases may not progress or progress only in sites of initial disease

Metastases are not always widely disseminated

Metastases do not always progress in multiple sites

Therefore there may be a role for local therapy in selected patients



Presented By Puneeth Iyengar at 2016 ASCO Annual Meeting

- 34/64 patients (53%) had all metastatic sites technically eligible for SBRT
- Local progression only
  - –64%
- Distant progression only
  - –9%
- Local and Distant progression
  - –27%

Table III. Sites of disease in SBRT-eligible patients

| Site | Number of Lesions |
|---|---|
| Lung parenchyma | 39 |
| Lung hilum | 11 |
| Upper mediastinum | 8 |
| Subcarinal/Precarinal lymph nodes | 5 |
| Anterior mediastinum | 1 |
| Supraclavicular fossa | 1 |
| Adrenal gland | 1 |
| Axilla | 5 |
| Liver | 5 |
| Spine | 8 |
| Other axial skeleton | 7 |



## Radiation During/After 1st line Therapy for Good Actors? Current and Past Randomized Studies

No definitive, prospective study which has examined aggressive local therapy (SBRT) for limited volume metastatic disease in NSCLC has been completed. Some are now reaching completion but no OS data yet.

- NCCTG study – **conventional xrt** to 1-3 sites of metastatic disease after chemo (60/30fx or 45/15 fx) (Schild et al)
- Univ of Chicago study randomized pts with oligomets from NSCLC to SBRT during 3rd and 4th cycle of 1st line chemo (Vokes et al)
- Single arm phase II study using SBRT for metastatic disease in stage IV NSCLC currently open at Wake Forest (Urbanic et al)



## UTSW Study

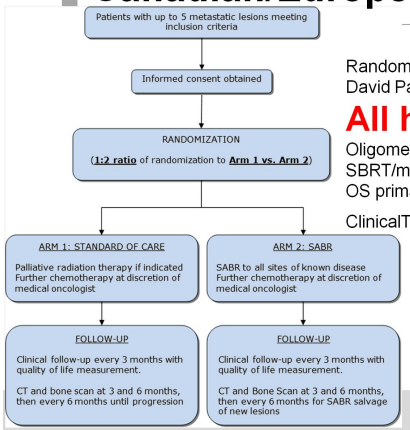
### Randomized Phase II Trial of Maintenance Chemotherapy vs. SBRT Followed by Maintenance Chemotherapy for Stage IV NSCLC

- **Hypothesis** – SBRT + maintenance chemotherapy will offer better PFS t maintenance chemo alone by promoting local control
- Most likely failure sites after 1st line therapy are in original sites of gross disease, hence the role sub-ablative SBRT may play in assisting systemic therapy with PFS
- Patients with limited metastatic NSCLC may have different biology than o stage IV patients with widely disseminated disease, therefore a potential benefit may exist to be more aggressive with this population



Presented By Puneeth Iyengar at 2016 ASCO Annual Meeting

## Canadian/European Study




Randomized Phase II European Trial
David Palma and Suresh Senan

**All histologies**

Oligometastatic disease – 1-3 and 4-5 lesions
SBRT/maint. vs maintenance therapy
OS primary endpoint

ClinicalTrials.gov Identifier: NCT01446744

OS from 9 months to 15 months
Pts +/- 1st line chemotherapy
Need 93 patients to have
$\alpha$ and $\beta$ of .20

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## MDACC Study

**A Randomized Phase II Study Assessing the Efficacy of Local Consolidative Therapy for Non-Small Cell Lung Cancer Patients With Oligometastatic Disease**

This study is ongoing, but not recruiting participants.

Sponsor:
M.D. Anderson Cancer Center

Information provided by (Responsible Party):
M.D. Anderson Cancer Center

ClinicalTrials.gov Identifier:
NCT01725165

First received: November 8, 2012
Last updated: February 2, 2016
Last verified: February 2016
History of Changes

**PFS benefit significant, limited number of patients received surgery but most radiation**

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## Proposed Randomized Phase II Study

NRG ONCOLOGY

NRG LU002
*(ClinicalTrials.gov NCT #)*

**MAINTENANCE CHEMOTHERAPY VERSUS CONSOLIDATIVE STEREOTACTIC BODY RADIATION THERAPY (SBRT) PLUS MAINTENANCE CHEMOTHERAPY FOR LIMITED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED PHASE II TRIAL**

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## Schema of Phase II Study

**NRG-LU002**
**SCHEMA**

Pemetrexed, Docetaxel, Erlotinib

| | | | | |
|---|---|---|---|---|
| Metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy<br><br>Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT. | STRATIFY | **Histology:**<br><br>Squamous vs. Non-squamous | RANDOMIZE | Arm 1:<br>Maintenance chemotherapy alone<br><br>Arm 2:<br>SBRT to all sites of metastases (≤ 3 discrete sites) plus irradiation of the primary site (SBRT or hypofractionated RT) followed by maintenance chemotherapy |

* Randomization will be 2:1 between Arm 2 and 1.

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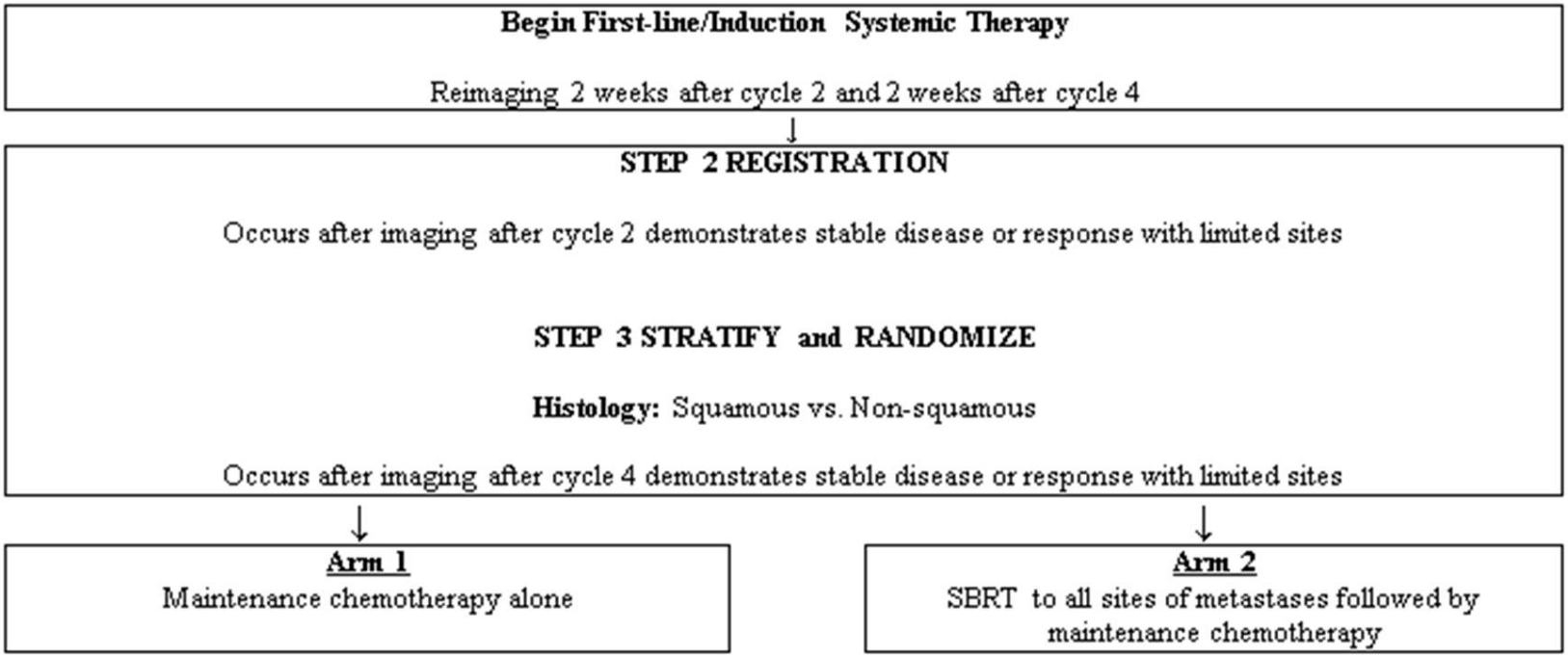
# NRG LU002




**An overall sample size of 170 eligible patients (85 patients in the maintenance chemotherapy arm and 85 patients in the SBRT + maintenance chemotherapy arm) achieves 85% power at a 0.05 significance level (1-sided) to detect a hazard ratio of 0.59 when the median overall survival (OS) times are 13 and 22 months in the maintenance group and SBRT treated group, respectively.**

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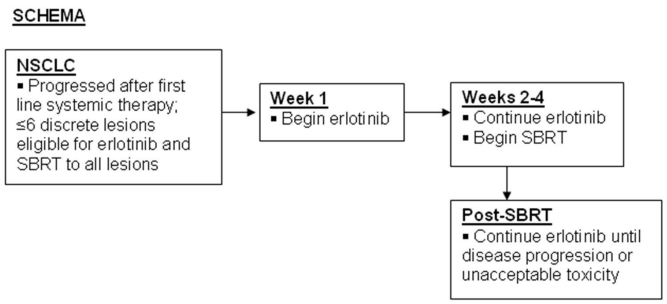
## Oligoprogression

1) UTSW/U Colorado experience

2) Canadian/David Palma study



## Schema

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## Summary

- 24/24 patients enrolled to trial
- All patients progressed through platinum based therapy
- SBRT was most frequently delivered to 3 or fewer sites/pt
- Lung parenchyma and mediastinal nodes most common sites
- Liver most common site of distant failure
- Very limited toxicity attributable to SBRT
- Median PFS 14.7 months, median OS 20.4 months
- 13 pts alive after last evaluation

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# New RCT for NSCLC Oligo-progression

**Stereotactic Radiotherapy for Oligo-Progressive Non-Small Cell Lung Cancer (STOP-NSCLC)**

**This study is not yet open for participant recruitment.** (see Contacts and Locations)

*Verified May 2016 by Lawson Health Research Institute*

**Sponsor:**
Lawson Health Research Institute

**Information provided by (Responsible Party):**
David Palma, Lawson Health Research Institute

**ClinicalTrials.gov Identifier:**
NCT02756793

First received: April 28, 2016
Last updated: May 4, 2016
Last verified: May 2016
History of Changes

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Presented By Puneeth Iyengar at 2016 ASCO Annual Meeting

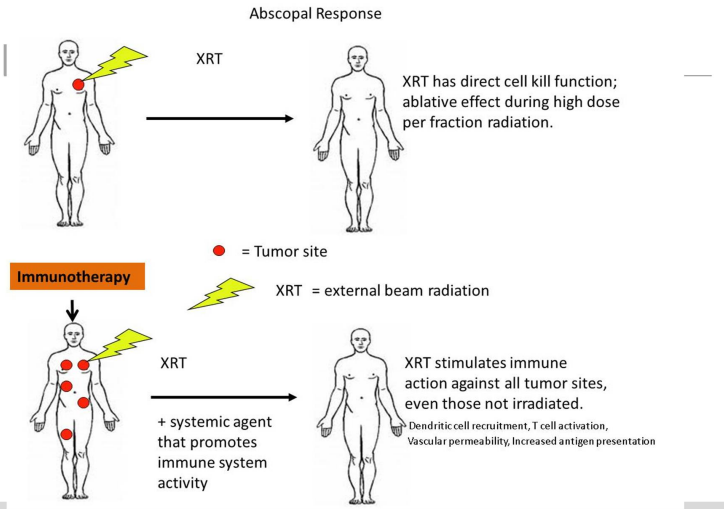
# Abscopal Response

Historically agreed that widely metastatic NSCLC would only receive local treatment in the form of radiation as palliation.

Should we be reassessing this view in light of abscopal responses in other disease sites

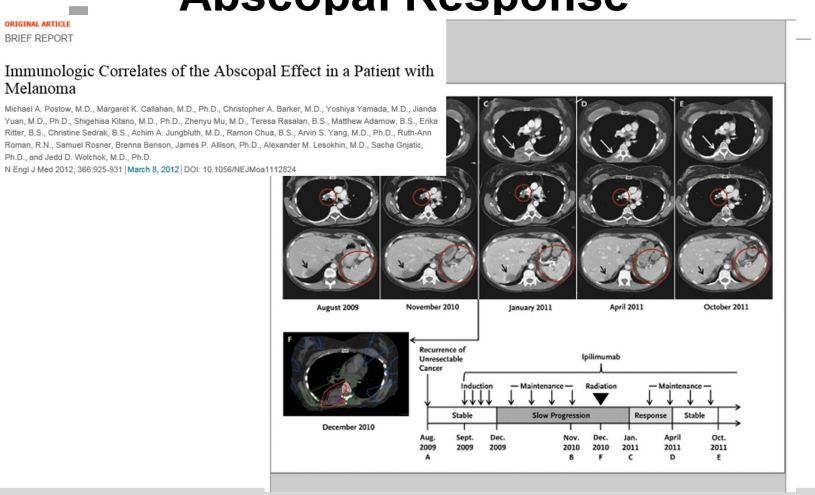
1) NEJM case report for melanoma
2) Abscopal responses from RCC
3) An increased interest in this phenomenon
4) Formenti trial
5) Science Translational Medicine study








# Abscopal Response


ORIGINAL ARTICLE
BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N Engl J Med 2012; 366:925-931 | March 8, 2012 | DOI: 10.1056/NEJMoa1112824





# Final Thoughts

SBRT for LMD is safe, feasible, and potentially beneficial to survival

Do LMD patients have different survival/biology than widely disseminated patients?

Does abscopal response exist in NSCLC states?

How do we define LMD?

# Tratamiento local en estadio IV: SBRT vs Cirugía

- Consolidación: se está "consolidando" como una alternativa a mantenimiento de QT o cambio a una 2ª línea.
- Oligoprogresión: Lo mismo, es una manera de retrasar el tratamiento sistemico o incluso de evitarlo.
- Abscopal: Serán como las meigas "Haberlas haylas", apuntan a que puede existir. Pero hay que combinarla con Inmunoterapia

**Local Consolidative Therapy (LCT) Improves Progression-Free Survival (PFS) in Patients with Oligometastatic Non-Small Cell Lung Cancer (NSCLC) who do not Progress after Front Line Systemic Therapy (FLST): Results of a Multi-Institutional Phase II Randomized Study**

Daniel Gomez, George Blumenschein, Jack Lee, Mike Hernandez, Ross Camidge, Robert Doebele, Laurie Gaspar, Don Gibbons, Jose Karam, Brian Kavanagh, Alexander Louie, David Palma, Anne Tsao, William William, Jianjun Zh Swisher*, John Heymach*, *on behalf of the MD Anderson Cancer Cen Moon Shot Initiative*

*Co-senior authors




# Trial Design

- Three participating institutions: 1) MD Anderson Cancer Center, 2) University of Colorado, 3) London Health Sciences Center
- Study opened in 12/2012
- Major eligibility criteria:
  - 1) Histologic confirmation of NSCLC
  - 2) AJCC 7th Edition Stage IV Disease
  - 3) No RECIST progression after front line systemic therapy (FLST)
  - 4) ≤3 metastasis after FLST (N1-N3 included as 1 site in setting of stage IV disease)
  - 5) No malignant pleural effusion



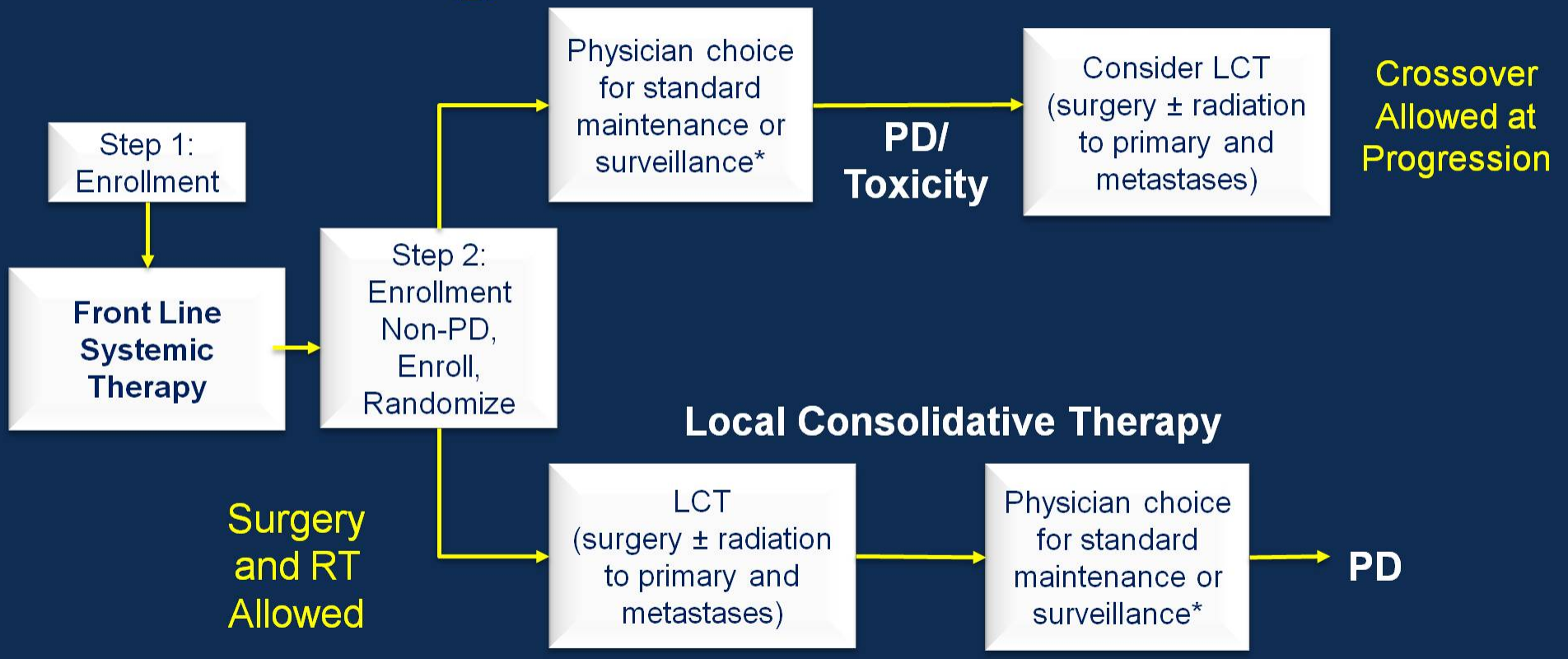


# Trial Design

Definition of FLST:

- ≥4 cycles of platinum-doublet chemotherapy
- ≥3 months of erlotinib, afatinib, or gefitinib therapy if EGFR mutation
- ≥3 months of crizotinib therapy if EML4-ALK fusion

# Trial Design



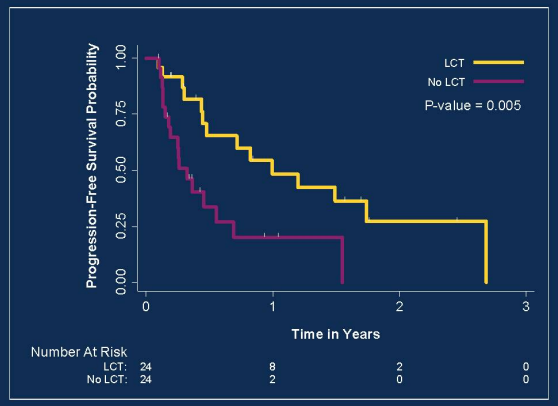
# Randomization

Balanced on 5 prognostic covariates

- Nodal status (N0/N1 vs. N2/N3)
- EGFR/EML4-ALK status (yes/no)
- Response to FLST (SD vs. PR/CR)
- CNS metastases (yes/no)
- Number of metastases (1 vs. 2/3)



# PFS Outcomes (updated data)




**One patient inevaluable (24 in each group)**

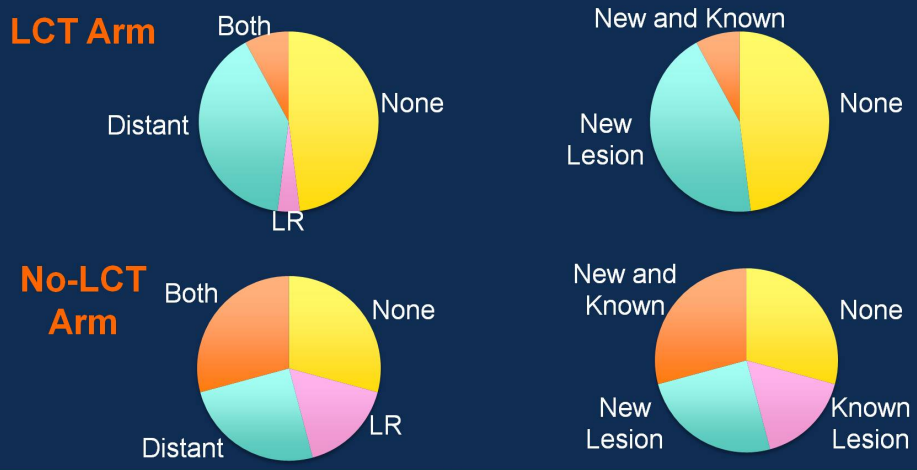
**Median PFS times:**

**No-LCT arm: 3.9 months (95% CI 2.2-6.6 months)**

**LCT arm: 11.9 months (95% CI 5.4 months-NA)**



# Patterns of Failure by Treatment Arm



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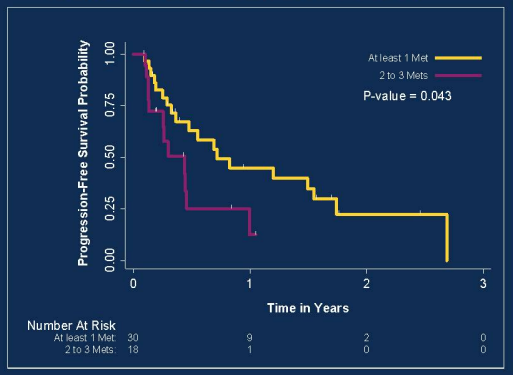
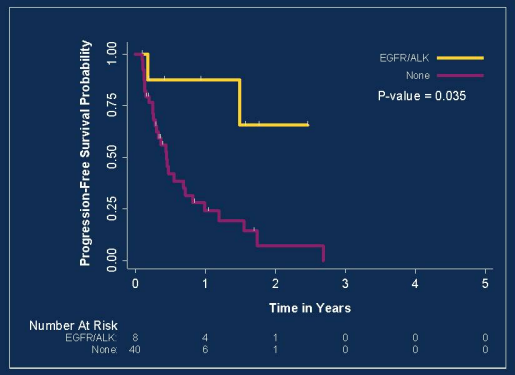
# Prognostic Factors for PFS

- Two other factors associated with PFS:

**Number of Mets after FLST**




**EGFR/ALK Status**








# Overall Survival

- 14 total deaths in the study (6 in LCT arm, 8 in no LCT arm)
- Median OS time was not reached in either arm
- Data not yet mature, patients continue to be followed for this endpoint

PRESENTED AT: ASCO ANNUAL MEETING '16
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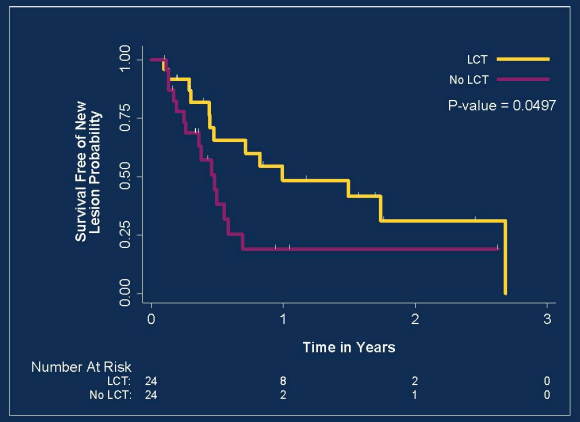
Presented by: Daniel Gomez, M.D.

# Toxicity

- No substantial difference in toxicity between 2 arms:
  - No-LCT arm – Three patients crossed over due to toxicity
    - 1 with fatigue, 1 with renal insufficiency, 1 with anemia
    - Additional patient with bilateral LE edema that warranted discontinuation
  - LCT arm
    - 2 patients with Grade 3 esophagitis, 1 anemia, 1 admission for pain, 1 pneumothorax




# Time to New Site Failure (TNSF)




**Median TNSF time 11.9 months in LCT arm vs. 5.7 months in no-LCT arm (p=0.0497)**

# Conclusions

- In patients with oligometastatic NSCLC who do not progress after FLST, LCT associated with improved PFS
- Exploratory Analysis - LCT also increased time to development of new lesions – suggests reduction in metastatic spread
- LCT with acceptable toxicity and without substantial differences in toxicity compared to no-LCT arm
- OS data not yet mature, patients continue to be followed

# Conclusions

- Limitations:  small size of study, patient/treatment heterogeneity, selected subset represented
- Study feasibility demonstrated - correlative studies and future trials will further attempt to elucidate which patient subsets benefit most from LCT

# Use of Stereotactic Radiosurgery in Treating Brain Metastases: Is There a Role for Whole-Brain Radiation Therapy?

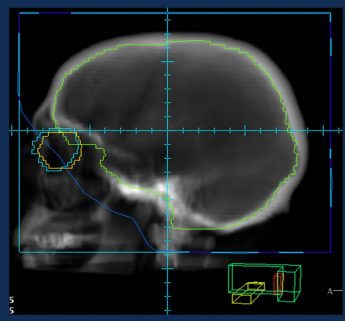
Paul Brown, MD
Professor Radiation Oncology
UT MD Anderson Cancer Center

No significant financial interest or affiliations to disclose
There will be discussion of off-label use of memantine




## Background

- Whole-Brain Radiation Therapy (WBRT) can treat numerous small lesions
- WBRT used decades
  - Little change in technique overtime
  - Remains the "go to treatment" for majority of brain mets



Chao Cancer 1954



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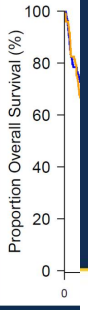



# Adjuvant WBRT

- Adding WBRT no impact on survival
- Adding WBRT worse cognitive function and QOL
- No role for WBRT if SRS is feasible

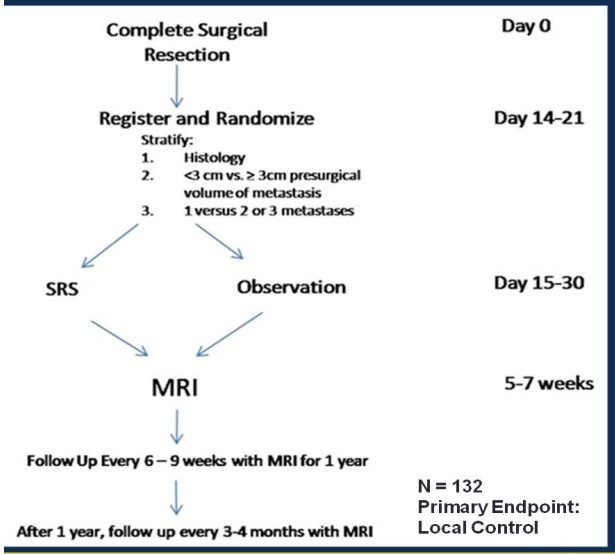
# Adjuvant WBRT after Resection

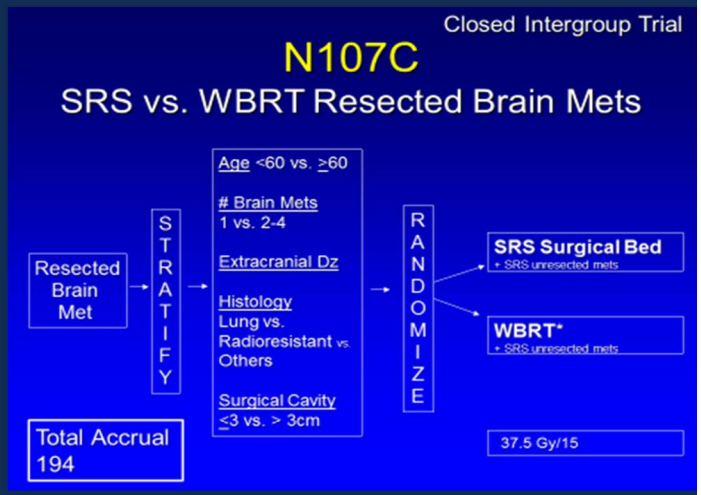
- Surgery indicated large lesions, mass effect good performance patients
- Resection alone high rate new brain mets and recurrence in surgical bed
- Adding WBRT significantly improves intracranial control
  - However WBRT impacts cognitive function
  - Growing interest SRS surgical cavity





# Adjuvant RT after Resection



## Cost Effectiveness SRS Alone

- No diff survival
- Salvage Therapy
  - 43% SRS alone
  - 26% SRS + WBRT




## JLGK0901 Prospective SRS Trial

- 1194 brain met pts
  - 1-10 brain mets
  - <10cc + <3cm
  - Total vol <15 cc
- SRS alone
- 92% Died Systemic Disease Progression

| | Median OS |
|---|---|
| 1 met | 14 months |
| 2-4 mets | 11 months |
| 5-10 mets | 11 months |



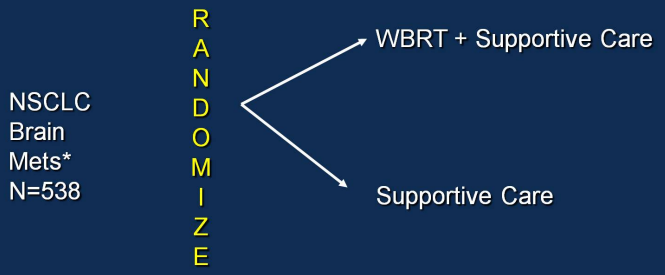
## Radiosurgery vs. WBRT

Multiple (>3) Brain Metastases

- No prospective phase III trials
- SRS disadvantage
  - Does not address micrometastases
  - More labor intensive
- SRS advantage
  - Less acute toxicity
  - Less delay systemic therapy
  - Likely less cognitive impact

## Palliative WBRT

Quartz Trial




ble for resection or SRS. 38% KPS < 70. WBRT 20Gy/5.



## Palliative WBRT

Quartz Trial

| | OS | QALY* |
|---|---|---|
| WBRT | 65 days | 43 days |
| Support | 57 days | 41 days |

- No difference in steroid use overtime
- No benefit WBRT in poor prognosis brain met patients

*QALY, quality adjusted life years, generated from OS and patients' weekly completion of the EQ-5D questionnaire.

# Indications for WBRT

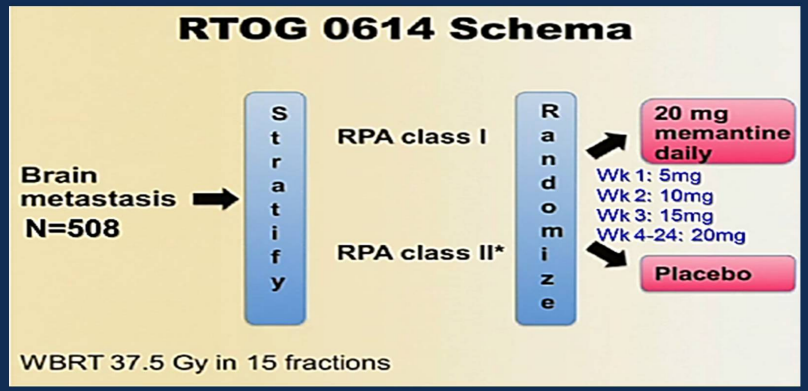
- Numerous lesions
  - Systemic Therapy?
- Lesions too large for radiosurgery and not surgical candidates
  - Fractionated radiosurgery?
- After surgical resection?

# Future Directions

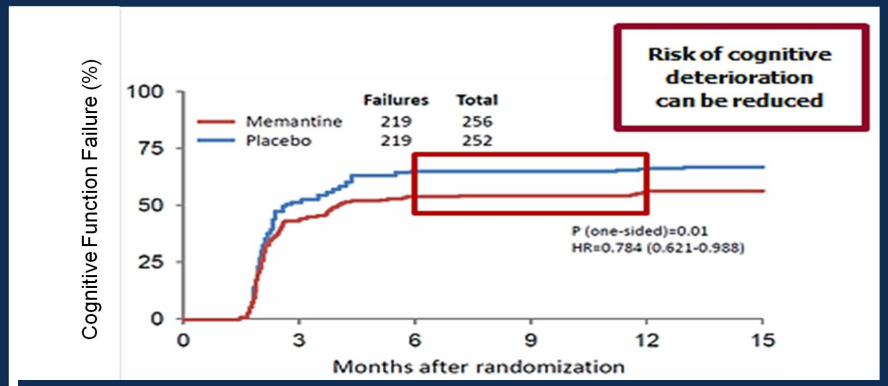
- WBRT 1950's Treatment
  - cobalt-60 new and state of the art
- Chemotherapy
  - Nitogen Mustard, MTX, Vincristine
  - No adjuvant or combination chemo
- Imaging
  - Angiogram
  - Pneumoencephalography




# WBRT +/- Memantine



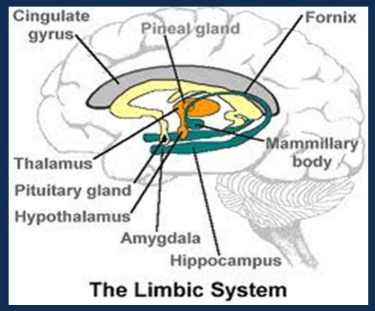

# WBRT +/- Memantine




# Cognitive Function

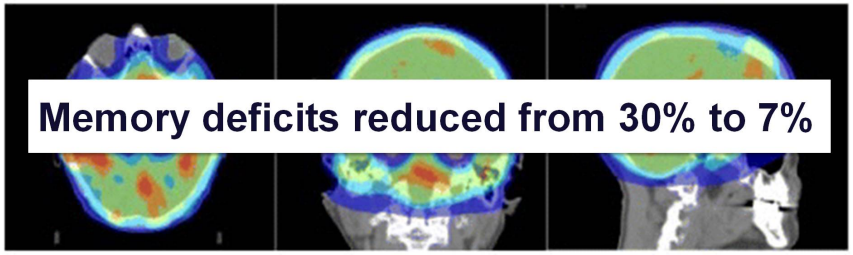
## Hippocampal Avoidance

- Hippocampal neurogenesis vital to memory
  - Hippocampal stem cells sensitive to RT
- Conformal avoidance hippocampus may reduce cognitive deficits



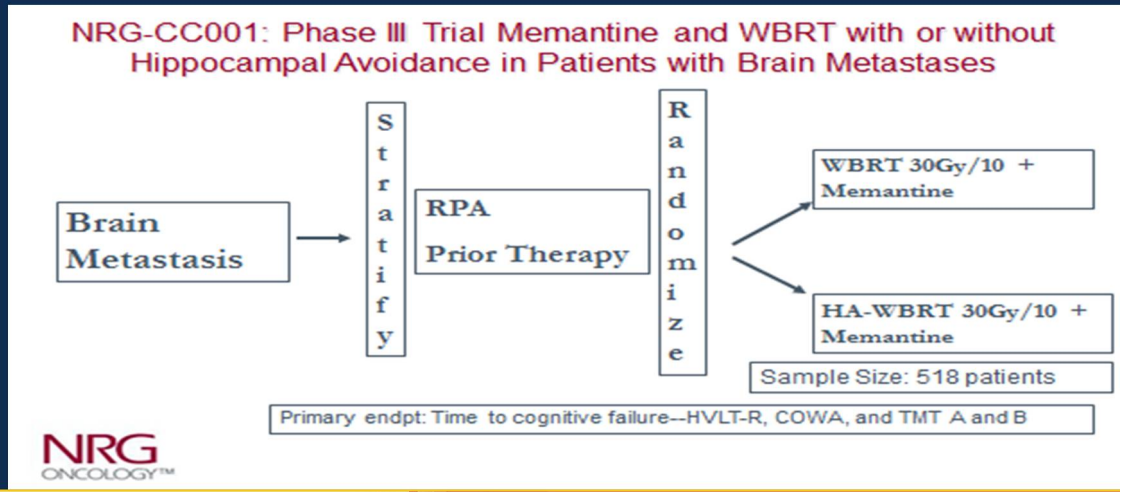

# Cognitive Function

## Hippocampal Avoidance Phase II RTOG 0933



# Cognitive Function

## Hippocampal Avoidance






# Conclusions

- The role for radiosurgery is growing
- The role for WBRT is diminishing
- The impact of WBRT on both cognitive function and QOL is now better understood
- Techniques/treatments to lesson toxicity of WBRT are needed
  - Support ongoing research (e.g. HA-WBRT Trial CC001)

# La proscrita RT holocraneal

- Adyuvante: Ni a la cirugía ni a la RC. Ojo a un posible aumento de las carcinomatosis tras cirugía.
- Paliativa: Hay que individualizar la indicación ya que según el trabajo comentado obtiene resultados similares a tratamiento sintomático paliativo.
- Futuro: Protección del hipocampo,¿?, Uso de memantina

# IMAGING AND CLINICAL ENDPOINTS IN BRAIN METASTASES TRIALS

**Riccardo Soffietti**

Professor and Chairman, Dept. Neuro-Oncology, University and City of Health and Science Hospital, Torino, Italy




## SPECIAL SITUATIONS : TREATMENT-RELATED CHANGES FOLLOWING SYSTEMIC TREATMENTS

- Pseudoresponse after treatment with antiangiogenic agents (especially anti-VEGF compounds) → reduction of enhancement and edema on MRI due to a normalization of vascular permeability, but no impact on neoangiogenesis and tumor growth.
- Pseudoprogression, increase in number of lesions, delayed responses after immunotherapy : in case of a patient neurologically stable treatment to be continued.
- In both instances importance of close confirmatory MRI scans



## SPECIAL SITUATIONS : TREATMENT-RELATED CHANGES FOLLOWING LOCAL THERAPIES

- Transient increase of enhancement on MRI after surgical resection → routine use of postoperative MRI to interpret subsequent MRI findings.
- Pseudoprogression and/or radionecrosis vs tumor regrowth after stereotactic radiosurgery → additive value of advanced neuroimaging techniques (MRI spectroscopy, MRI perfusion, PET with amminoacids or FLT), but still needing validation in prospective studies.

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# Seguimiento/Interpretación de las imágenes de la RM tras tratamientos locales

- Se hace necesaria una estrecha comunicación con neurorradiologos, medicina nuclear y los clínicos,  para el DD de pseudoprogresión, radionecrosis y recidiva. A todo esto se le va a añadir los efectos de los ITK y de la inmunoterapia. Luego la interpretación de las RM de control supondrán un esfuerzo añadido en el seguimiento


264