TOP THORACIC ONCOLOGY PADOVA
NON-SMALL CELL LUNG CANCER: FOCUS ON OLIGOMETASTATIC DISEASE AND 2017 UPDATE
March 31 - April 01, 2017
PADOVA

# *Update on locally advanced disease:*

# *Radiation Oncology*

**Filippo Alongi, MD**

Chair of Radiation Oncology Department
Sacro Cuore Don Calabria Cancer Care Center,
Negrar-Verona, Italy

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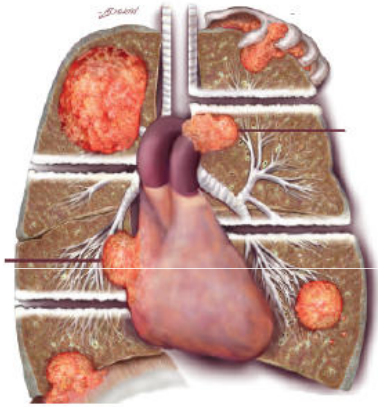
Cancer Care Center
Negrar - Verona

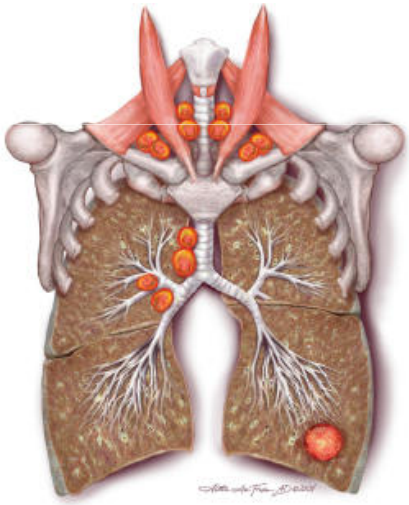
# *LOCALLY ADVANCED STAGE LUNG NSCLC:*
# *background*



***Staging of NCSLC***

"Stage III represents a very heterogeneus group."

| | | |
|---|---|---|
| **Stage IIIA** | T1, T2 | **N2** |
| | T3 | N1,**N2** |
| | T4 | N0, N1 |
| **Stage IIIB** | ogni T | **N3** |
| | T4 | **N2** |



***Objectives:*** **Stage III non-small cell lung cancer (NSCLC) describes a heterogeneous population with disease presentation ranging from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky nodal disease.**

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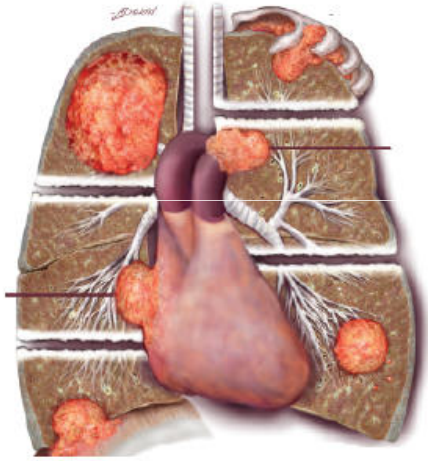
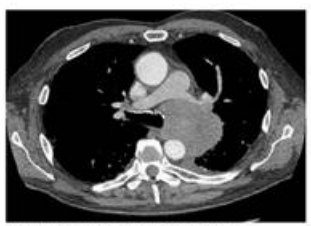
# LOCALLY ADVANCED STAGE LUNG NSCLC:
## *Treatment options*

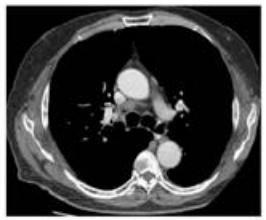


## Treatment of Stage III Non-small Cell Lung Cancer

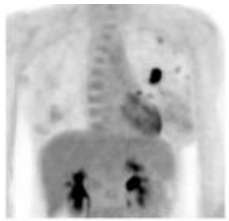
**Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**



Mediastinal Infiltration

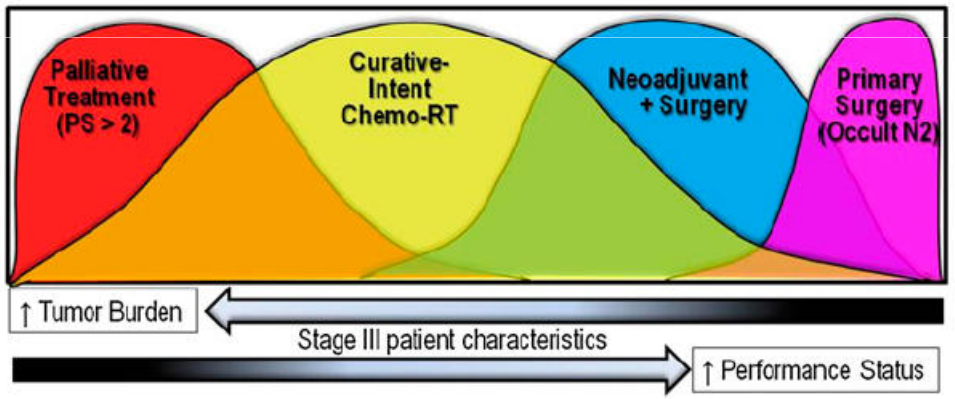


Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches

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CHEST 2013; 143(5)(Suppl):e314S–e340S

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# LOCALLY ADVANCED STAGE LUNG NSCLC:
## *Radiotherapy*

CANCER INVESTIGATION
2016, VOL. 0, NO. 0, 1–14

## What is changing in radiotherapy for the treatment of locally advanced nonsmall cell lung cancer patients? a review

Niccoló Giaj-Levra, Francesco Ricchetti, and Filippo Alongi

Radiation Oncology, Sacro Cuore-Don Calabria Hospital, Negrar-Verona, Italy

**ABSTRACT**

Radiotherapy treatment continues to have a relevant impact in the treatment of nonsmall cell cancer (NSCLC). Use of concurrent chemotherapy and radiotherapy is considered the gold standard in the treatment of locally advanced NSCLC but clinical outcomes are not satisfactory. Introduction of new radiotherapy technology and chemotherapy regimens are under investigation in this setting with the goal to improve unsatisfactory results. We report how radiotherapy is changing in the treatment of locally advanced NSCLC.

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*Giaj-levra N et al. Cancer investigation 2016*

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# *LOCALLY ADVANCED STAGE LUNG NSCLC:*
## *Radiotherapy*


**From chemotherapy to target therapies associated with radiation in the treatment of NSCLC: a durable marriage?**

Filippo Alongi, Stefano Arcangeli, Sara Ramella, Niccolò Giaj-Levra, Paolo Borghetti, Rolando D'Angelillo, Francesco Ricchetti, Marta Maddalo, Rosario Mazzola, Marco Trovò, Elvio Russi & Stefano Maria Magrinion the behalf of Associazione Italiana Radioterapia Oncologica (AIRO)

- To date the addition of target therapies to chemo-radiotherapy did not demonstrate any robust advantage in this stage of disease.
- Chemo-radiotherapy still represents the standard of choice in locally advanced NSCLC

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*Alongi et al. Expert review in anticancer therapy 2017*

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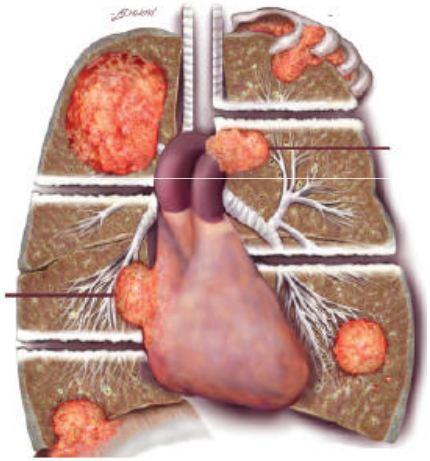
# LOCALLY ADVANCED STAGE LUNG NSCLC:

## *Radio(chemo)therapy*



1. Timing with Chemotherapy (concurrent, sequential)

2. Timing with Surgery: neoadjuvant versus adjuvant



CHEST 2013; 143(5)(Suppl):e314S–e340S

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# LOCALLY ADVANCED STAGE LUNG NSCLC:
## *Radio(chemo)therapy*

1. Timing with Chemotherapy (concurrent, sequential)

**Analysis 6.1. Comparison 6 concurrent versus sequential, Outcome 1 overall survival.**

Review: Concurrent chemoradiotherapy in non-small cell lung cancer

Comparison: 6 concurrent versus sequential

Outcome: 1 overall survival

| Study or subgroup | Concurrent n/N | Sequential n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Curran 2003 | 127/201 | 139/201 | | 49.7 % | 0.91 [ 0.79, 1.05 ] |
| Fournel 2001 | 67/103 | 80/104 | | 31.4 % | 0.85 [ 0.71, 1.01 ] |
| Zatloukal 2003 | 34/52 | 43/50 | | 18.9 % | 0.76 [ 0.61, 0.95 ] |
| **Total (95% CI)** | **356** | **355** | | **100.0 %** | **0.86 [ 0.78, 0.95 ]** |

Total events: 228 (Concurrent), 262 (Sequential)
Heterogeneity: Tau² = 0.0; Chi² = 1.90, df = 2 (P = 0.39); I² =0.0%
Test for overall effect: Z = 2.96 (P = 0.0031)


OS

**RT-CHT increases OS and PFS**

**Analysis 6.2. Comparison 6 concurrent versus sequential, Outcome 2 locoregional progression-free survival.**

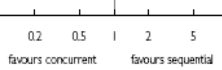
Review: Concurrent chemoradiotherapy in non-small cell lung cancer

Comparison: 6 concurrent versus sequential

Outcome: 2 locoregional progression-free survival

| Study or subgroup | Concurrent n/N | Sequential n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Curran 2003 | 64/201 | 76/201 | | 100.0 % | 0.84 [ 0.64, 1.10 ] |
| **Total (95% CI)** | **201** | **201** | | **100.0 %** | **0.84 [ 0.64, 1.10 ]** |

Total events: 64 (Concurrent), 76 (Sequential)
Heterogeneity: not applicable
Test for overall effect: Z = 1.25 (P = 0.21)




PFS

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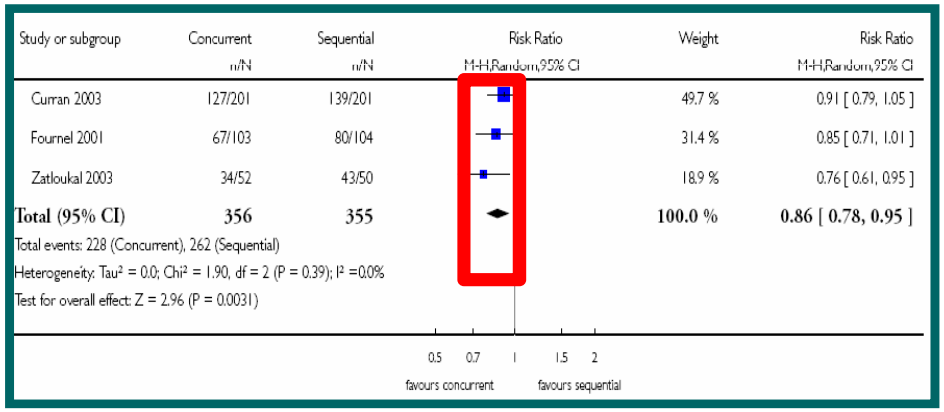
# ADVANCED STAGE LUNG NSCLC:
## *Radio(chemo)therapy*

1. Timing with Chemotherapy (concurrent, sequential)



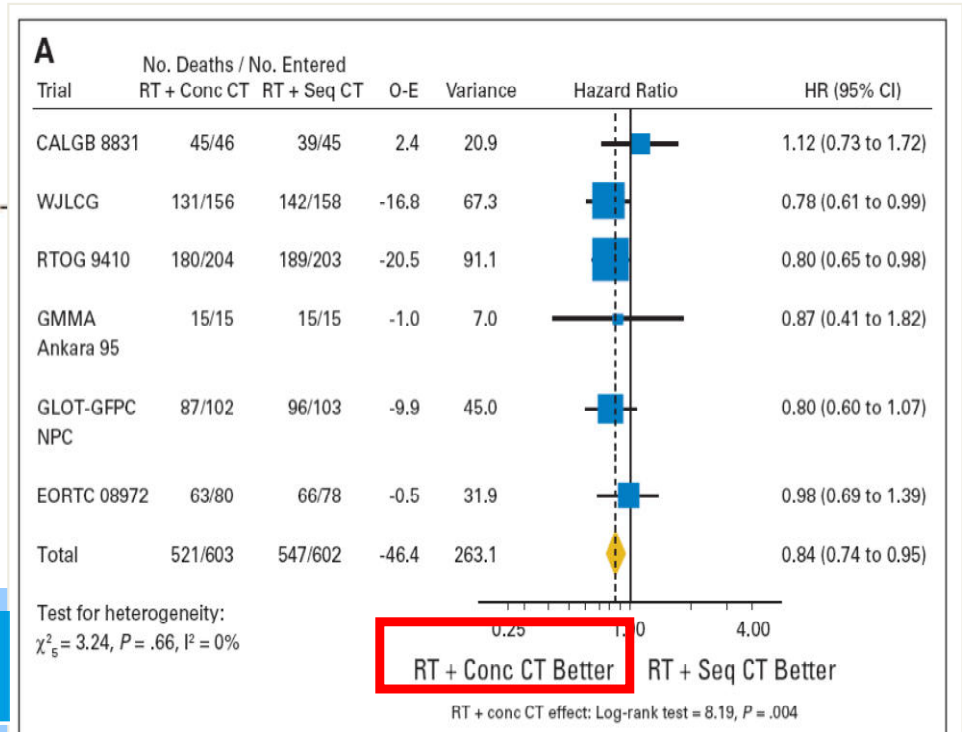

***RTCHT:***
***2-y Risk of Death Reduction 14%***

*O´Rourke N. Clin Oncol 2010*

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Lung Cancer

***RTCHT:***

*Increase 3 and 5-y OS of* ***5.7% and 4.5%, respectively***

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# ADVANCED STAGE LUNG NSCLC:
## *Radio(chemo)therapy*

Table 5. Concurrent versus sequential chemoradiotherapy : toxicity (grade 3 to 5)

| trial | deaths | acute oesophagitis | acute pneumonitis | late oesophagitis | lung fibrosis | neutropenia | anaemia |
|---|---|---|---|---|---|---|---|
| | number of deaths / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential | number of cases / number assessable; concurrent v sequential |
| Curran 2003 | 6/201 v 4/201 | 50/201 v 8/201 | 8/201 v 14/201 | not reported | 22/201 v 26/201 | 117/201 v 113/201 | not reported |
| Fournel 2001 | 10/89 v 6/89 | 0/89 v 23/89 | not reported | not reported | not reported | 67/89 v 78/89 | not reported |
| Zatloukal 2002, 2003 | 0/52 v 0/50 | 9/52 v 2/50 | 2/52 v 1/50 | not reported | not reported | 34/52 v 20/50 | not reported |
| total | 16/342 v 10/340 (4.7% v 2.9%) | 59/342 v 33/340 (17.3% v 9.7%) | 10/253 v 15/251 (4.0% v 6.0%) | - | 22/201 v 26/201 (10.9% v 12.9%) | 217/342 v 210/340 (63.4% v 61.8%) | - |
| relative risk (P; Fisher's Exact Test) | 1.59 (NS) | 1.78 P=0.004 | 0.66 (NS) | - | 0.85 (NS) | 1.03 (NS) | - |

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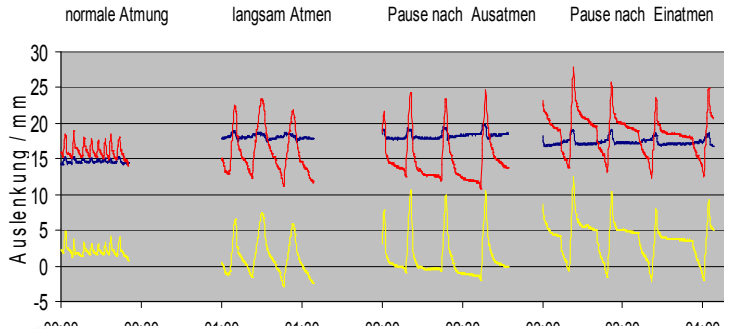
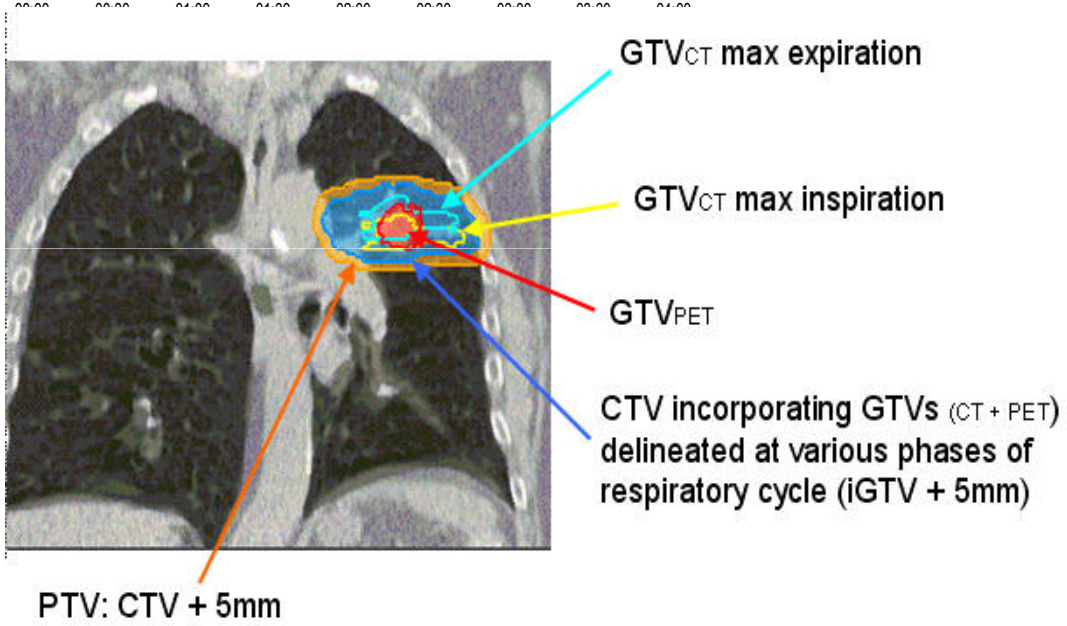
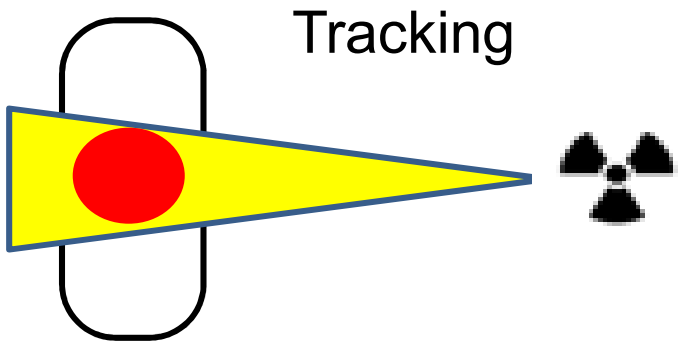
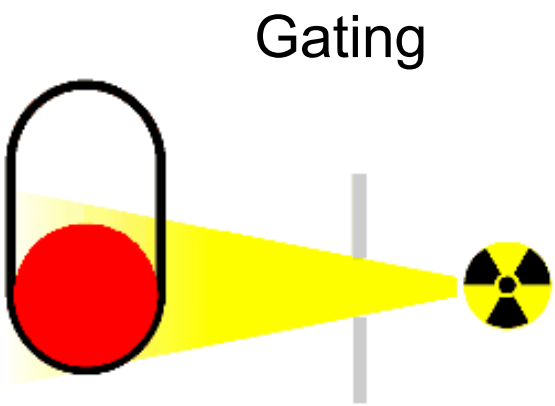
# ADVANCED STAGE LUNG NSCLC:
# ADVANCEMENTS IN RADIATION ONCOLOGY

## THE ISSUE OF MOTION MANAGEMENT



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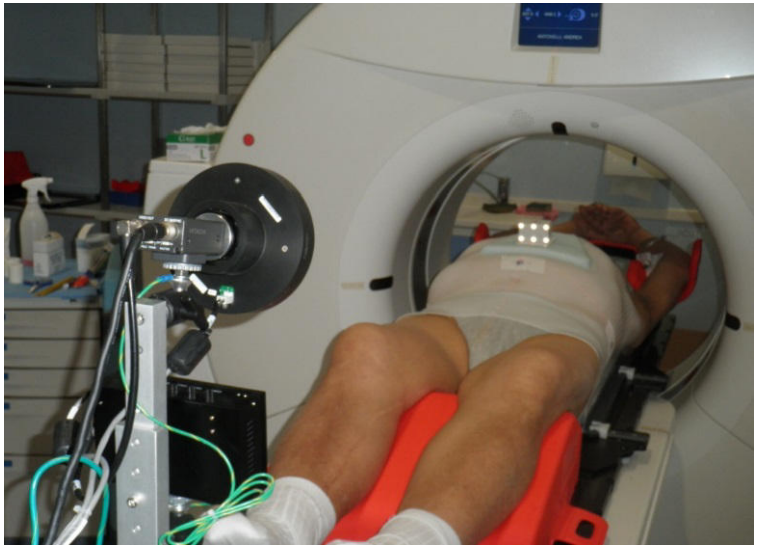
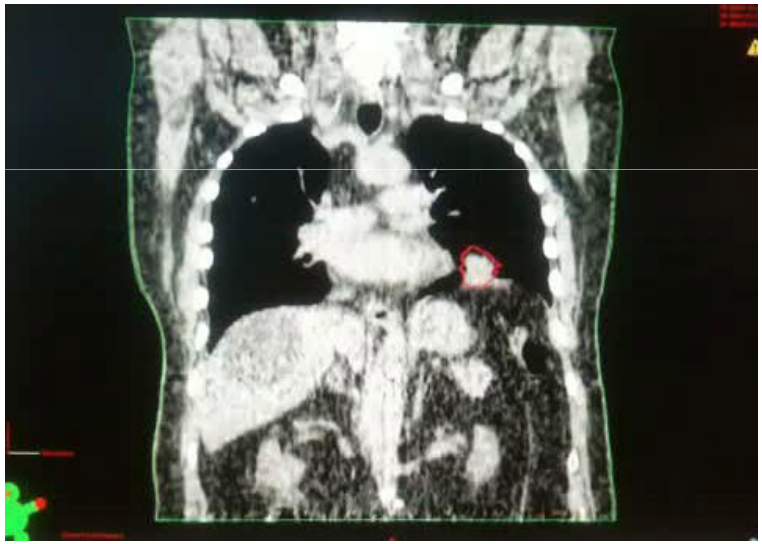
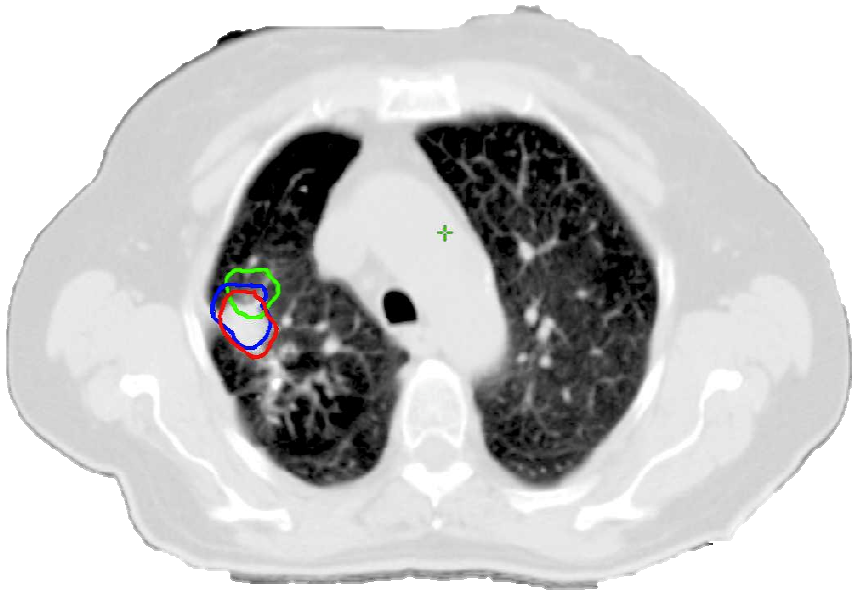
# *ADVANCED STAGE LUNG NSCLC:*
# *ADVANCEMENTS IN RADIATION ONCOLOGY*





## 4D CT AND MOTION MANAGEMENT



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# A CONTINUOUS CHANGING:
## *IMAGING ON BOARD (IGRT)*

Int J Clin Oncol (2009) 14:568–569
DOI 10.1007/s10147-009-0896-1



LETTER TO THE EDITOR

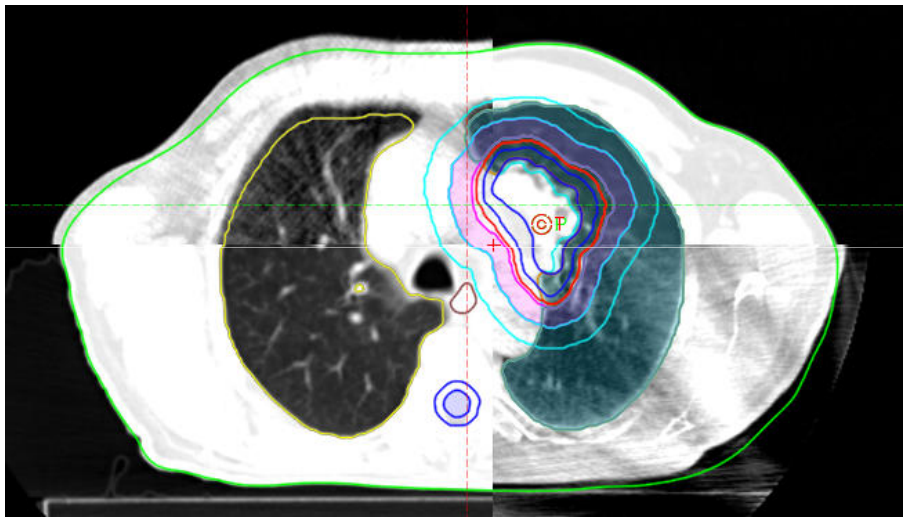
Filippo Alongi · Nadia Di Muzio

**Image-guided radiation therapy: a new era for the radiation oncologist?**

dimensional customized targets, after tumor targeting and organ contouring on each CT scan.

In the modern era of radiotherapy the term "image-guided radiation therapy (IGRT)" has encompassed the use of various types of images to control patient position in order to correct possible setup errors. IGRT uses weekly or

F. Alongi



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Alongi et al et al. Int.J Clin Oncol. 2009

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# ADVANCED STAGE LUNG NSCLC:
## IMRT/VMAT as Treatment options for chemo-RT

Scorsetti *et al. Radiation Oncology* 2010, **5**:94
http://www.ro-journal.com/content/5/1/94

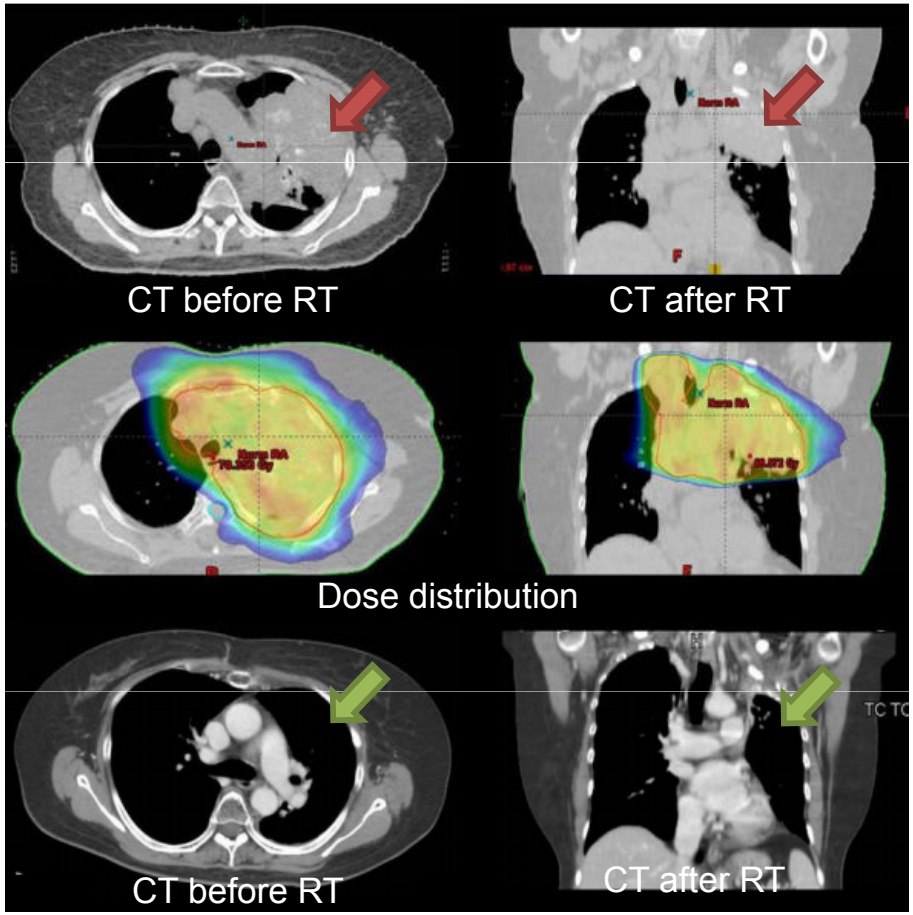
RADIATION ONCOLOGY

RESEARCH Open Access

### Large volume unresectable locally advanced non-small cell lung cancer: acute toxicity and initial outcome results with rapid arc

Marta Scorsetti[1], Pierina Navarria[1], Pietro Mancosu[1*], Filippo Alongi[1], Simona Castiglioni[1], Raffaele Cavina[2], Luca Cozzi[3], Antonella Fogliata[3], Sara Pentimalli[1], Angelo Tozzi[1], Armando Santoro[3]

Acute toxicities at 3 months showed:
-91% with grade 1
*-9% with grade2*
*-no Grade3*
esophageal toxicity






Scorsetti et al. Radiat Oncol. 2010

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# ADVANCED STAGE LUNG NSCLC:

## *IMRT as new standard Treatment option for chemo-RT*

# Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial


**Purpose**
Although intensity-modulated radiation therapy (IMRT) is increasingly used to treat locally advanced non–small-cell lung cancer (NSCLC), IMRT and three-dimensional conformal external beam radiation therapy (3D-CRT) have not been compared prospectively. This study compares 3D-CRT and IMRT outcomes for locally advanced NSCLC in a large prospective clinical trial.

**Patients and Methods**
A secondary analysis was performed to compare IMRT with 3D-CRT in NRG Oncology clinical trial RTOG 0617, in which patients received concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab, and 60- versus 74-Gy radiation doses. Comparisons included 2-year overall survival (OS), progression-free survival, local failure, distant metastasis, and selected Common Terminology Criteria for Adverse Events (version 3) ≥ grade 3 toxicities.

**Results**
The median follow-up was 21.3 months. Of 482 patients, 53% were treated with 3D-CRT and 47% with IMRT. The IMRT group had larger planning treatment volumes (median, 427 *v* 486 mL; $P = .005$); a larger planning treatment volume/volume of lung ratio (median, 0.13 *v* 0.15; $P = .013$); and more stage IIIB disease (30.3% *v* 38.6%, $P = .056$). Two-year OS, progression-free survival, local failure, and distant metastasis–free survival were not different between IMRT and 3D-CRT. IMRT was associated with less ≥ grade 3 pneumonitis (7.9% *v* 3.5%, $P = .039$) and a reduced risk in adjusted analyses (odds ratio, 0.41; 95% CI, 0.171 to 0.986; $P = .046$). IMRT also produced lower heart doses ($P < .05$), and the volume of heart receiving 40 Gy (V40) was significantly associated with OS on adjusted analysis ($P < .05$). The lung V5 was not associated with any ≥ grade 3 toxicity, whereas the lung V20 was associated with increased ≥ grade 3 pneumonitis risk on multivariable analysis ($P = .026$).

**Conclusion**
IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RTOG 0617, which supports routine use of IMRT for locally advanced NSCLC.


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Chun et al. J Clin Oncol. 2017 Jan;35(1):56-62

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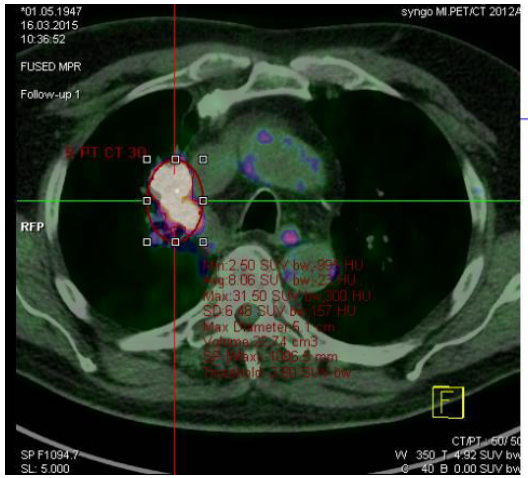
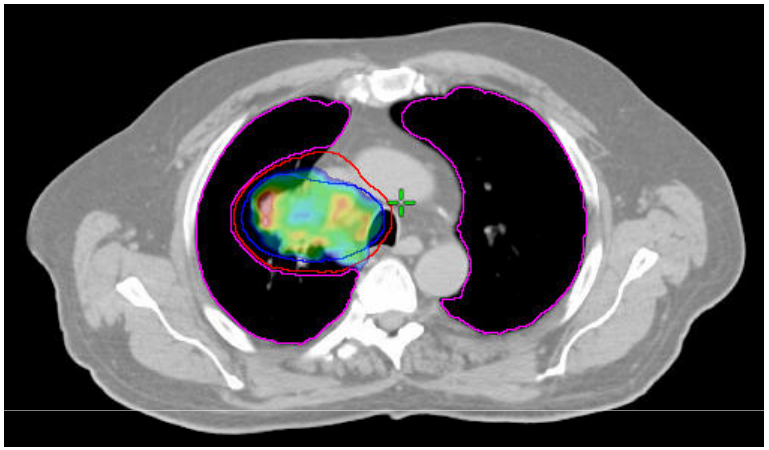
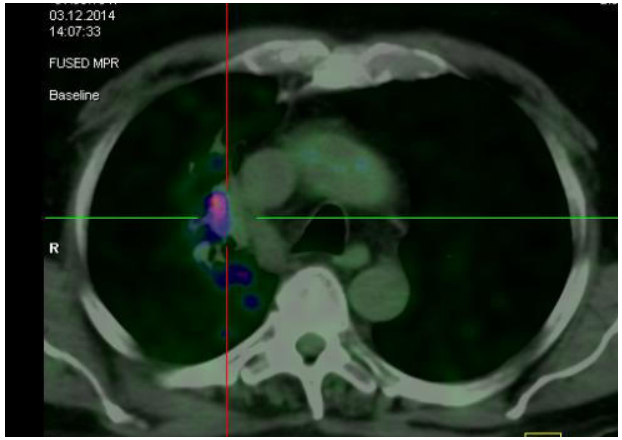
# ADVANCED STAGE LUNG NSCLC:

## *IMRT as new standard Treatment option for chemo-RT*

Treatment for Locally Advanced NSCLC






PET before RT

60 Gy/30 fr. with VMAT

PET after RT

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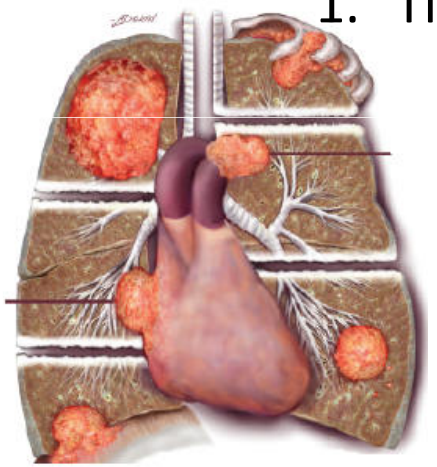
# *ADVANCED STAGE LUNG NSCLC:*
## *RT-CT final remarks*

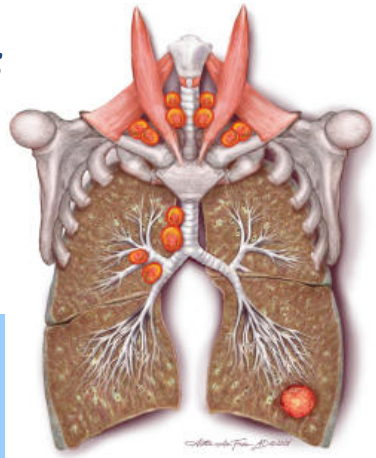


1. Timing with Chemotherapy (concurrent, sequential)

**Final remarks**

***Concurrent* chemoradiation *increased overall survival* and *progression free survival* compared to sequential treatment.**

***New intensity modulated and image guided RT techniques are suggested***



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# PDTA ROV


**•17) RADIOTERAPIA + CHEMIOTERAPIA**

•Stadio IIIA (T3 N1 - T4 per estensione N0-1) se non candidabili a chirurgia devono essere sottoposti a trattamento concomitante chemio-radioterapico. Il trattamento chemioterapico e radioterapico sequenziale o radioterapico esclusivo deve essere considerato nei pazienti fragili non in grado di tollerare concomitanza.

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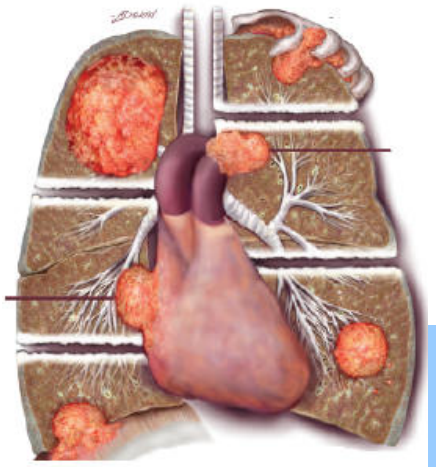
# *ADVANCED STAGE LUNG NSCLC:*
# *SURGERY? WHEN?*

1. Timing with Chemotherapy (concurrent, sequential)

2. Timing with Surgery: neoadjuvant versus adjuvant



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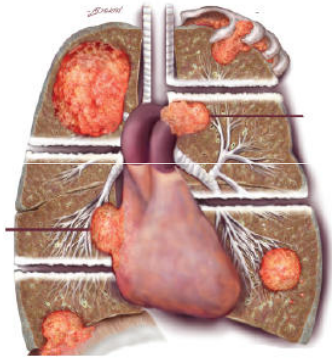
# *ADVANCED STAGE LUNG NSCLC:*
# *SURGERY? WHEN?*



## *Clinical N2 (cN2) Neoadjuvant therapy*

2. 3 RANDOMIZED TRIALS:

- ✓ INT 0139 *(Albain Lancet 2009)*
- ✓ GERMAN study *(Thomas Lancet Oncology 2008)*
- ✓ EORTC *(Van Meerbeeck J Natl Cancer Inst 2007)*

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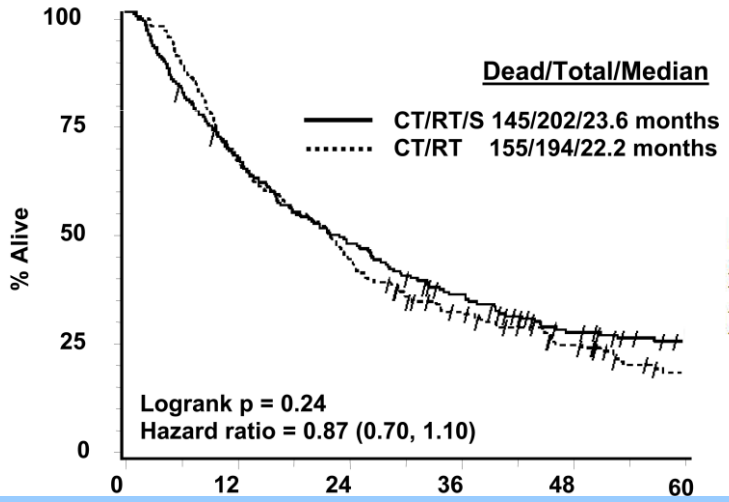
# ADVANCED STAGE LUNG NSCLC:
## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus adjuvant

✓ INT 0139 *(Albain Lancet 2009)*

**Methods—**Patients with stage T1-3pN2M0 NSCLC were randomized before induction chemoRT (2 cycles of cisplatin and etoposide [PE] concurrent with 45 Gy RT). If no progression, arm 1 underwent resection, and arm 2 continued RT uninterrupted to 61 Gy. Two additional cycles of PE were given. The primary endpoint was overall survival (OS).




**Interpretation—**There was no significant survival advantage to surgery after chemoRT, despite improved PFS. Both chemoRT with definitive RT and chemoRT followed by resection (preferably lobectomy) are options for patients with stage IIIA(N2) NSCLC.

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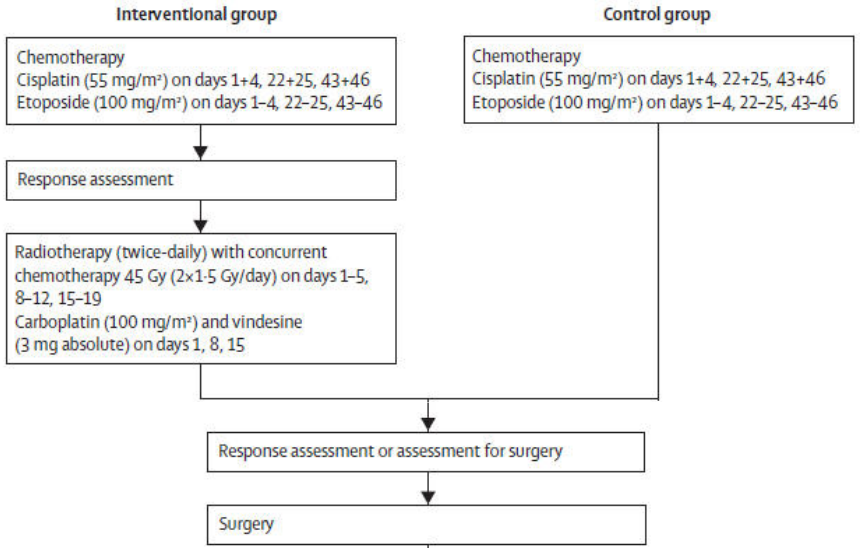
# ADVANCED STAGE LUNG NSCLC:
## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus adjuvant

✓ GERMAN study *(Thomas Lancet Oncology 2008)*

**Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer**

*Michael Thomas, Christian Rübe, Petra Hoffknecht, Hans N Macha, Lutz Freitag, Albert Linder, Norman Willich, Michael Hamm, Gerhard W Sybrecht, Dieter Ukena, Karl-Matthias Deppermann, Cornelia Dröge, Dorothea Riesenbeck, Achim Heinecke, Cristina Sauerland, Klaus Junker, Wolfgang E Berdel*, Michael Semik*, for the German Lung Cancer Cooperative Group***




**INTERPRETATION:** In patients with stage III NSCLC amenable to surgery, preoperative chemoradiation in addition to chemotherapy increases pathological response and mediastinal downstaging, but does not improve survival. After induction with chemoradiation, pneumonectomy should be avoided.



*Lancet Oncol* 2008; 9: 636–648

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# ADVANCED STAGE LUNG NSCLC:

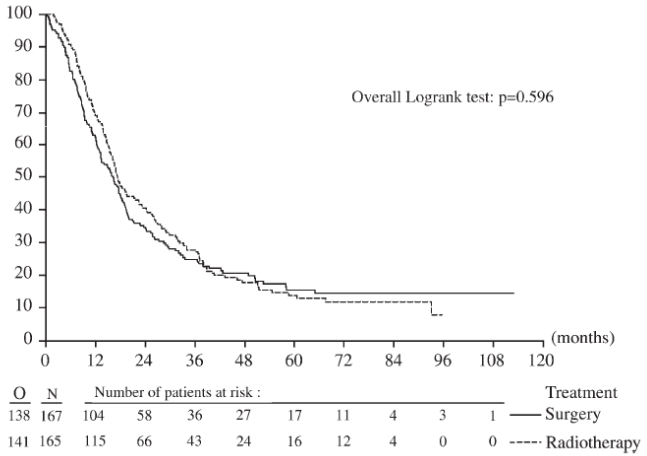
## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus adjuvant

✓ EORTC *(Van Meerbeeck J Natl Cancer Inst 2007)*

### Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone




## Conclusion

In selected patients with pathologically proven stage IIIA-N2 NSCLC and a response to induction chemotherapy, surgical resection did not improve overall or progression-free survival compared with radiotherapy. In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment for these patients.

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J Natl Cancer Inst 2007;99:442–50

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# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus adjuvant

### Final remarks

**3.5.2. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone** (Grade 1A).

**3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial)** (Grade 1C).

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*CHEST 2013; 143(5)(Suppl):e314S–e340S*

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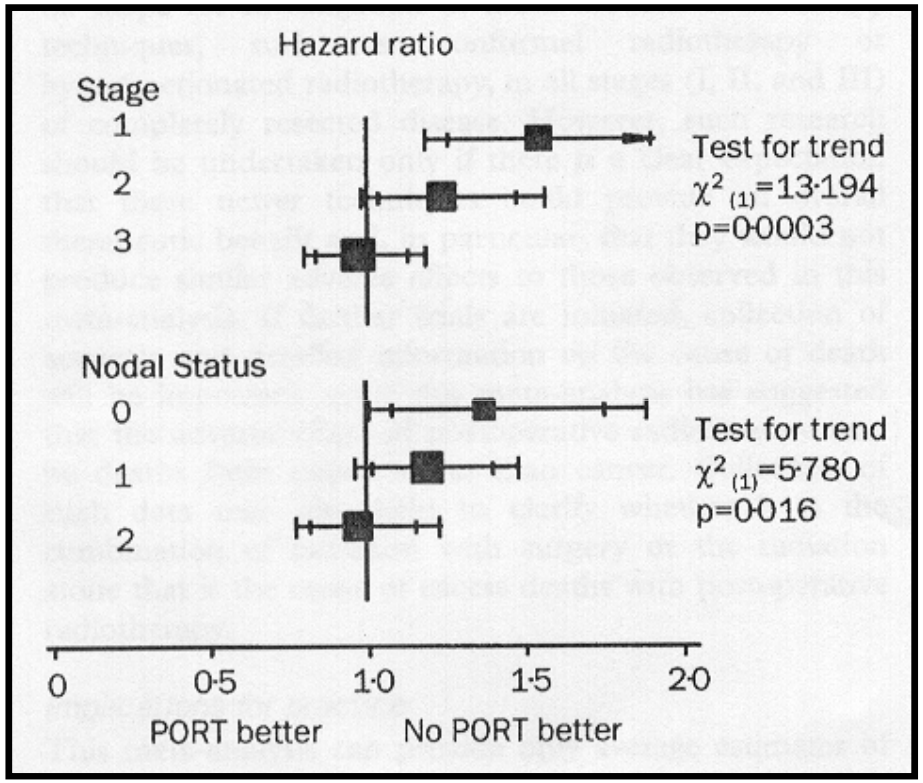
# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus **adjuvant**

**Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials**

*PORT Meta-analysis Trialists Group**




***Critical points of trials***

1. *Recruitment*
2. *Dose and fractionation*
3. *Volume*
4. *Technique*
5. *Technology*

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THE LANCET • Vol 352 • July 25, 1998

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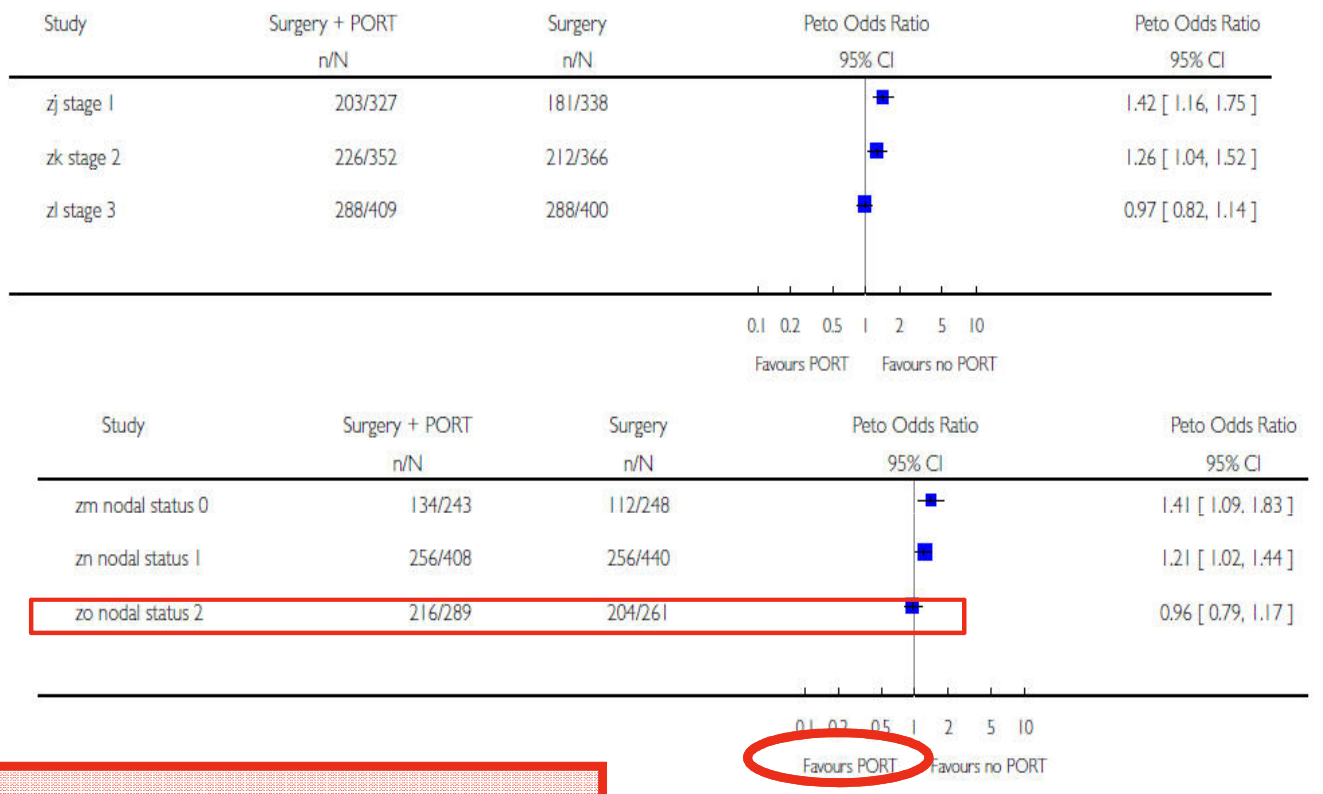
# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus **adjuvant**




THE COCHRANE COLLABORATION®

**Adjuvant RT increases PFS for N2 disease**

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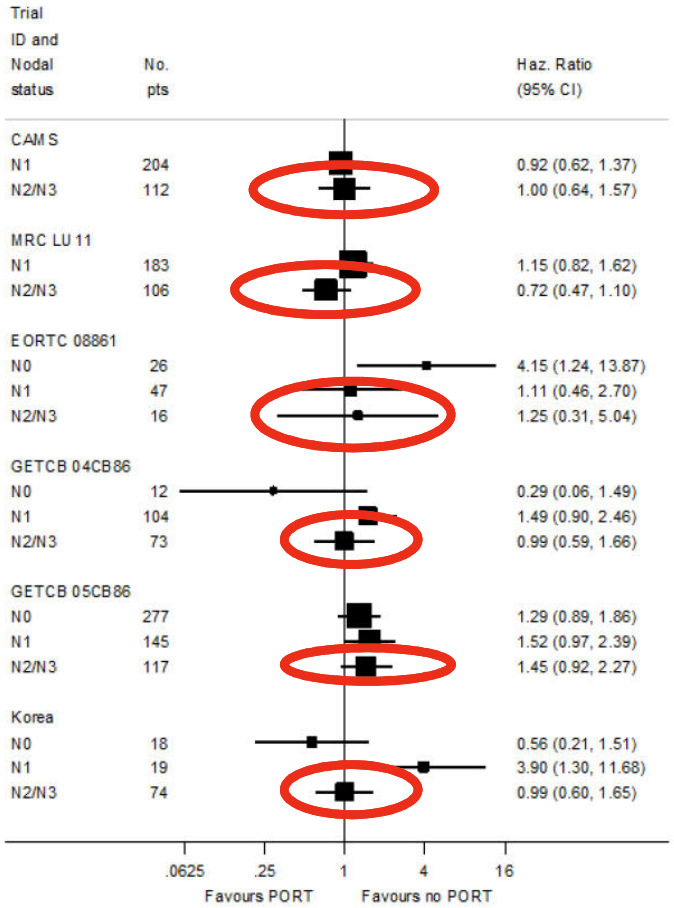
# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

Comparison Surgery + PORT versus surgery alone – Nodal status

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*PORT Meta-analysis Trialists Group** **2016**

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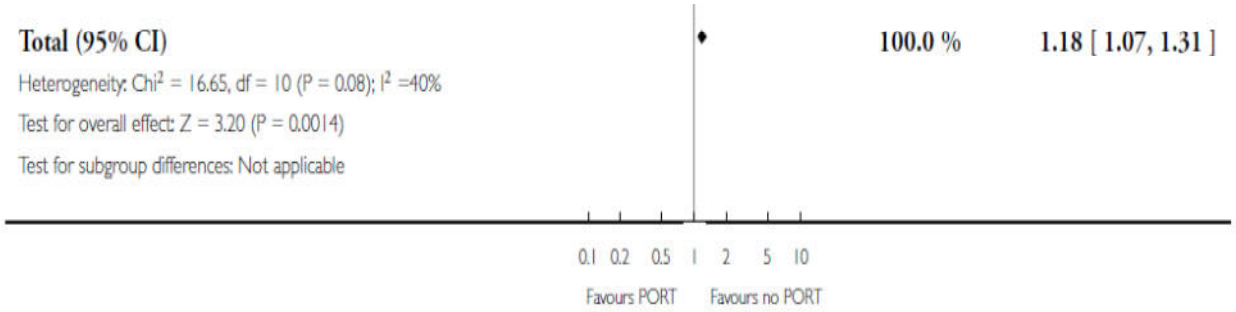
# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

Comparison Surgery + PORT versus surgery alone – Overall survival




## AUTHORS' CONCLUSIONS

### Implications for practice

Although the radiotherapy used in most of the included trials is now considered suboptimal, this update still provides the best evidence that postoperative radiotherapy (PORT) has an adverse effect on survival. There is now less compelling evidence that the effect of PORT varies by stage, and in particular nodal status, but PORT should not be used routinely unless supporting evidence can be obtained from an ongoing trial of modern PORT techniques (Lung ART-IGR 2006/1202).



*PORT Meta-analysis Trialists Group** **2016**

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# ADVANCED STAGE LUNG NSCLC:
## *Neoadjuvant vs adjuvant*

## PORT in N2 positive lymph node

| | Local Tumor Control | Disease-Free Survival | Cancer-Specific Survival |
|---|---|---|---|
| **Single/ Multiple pN2** | Odds ratio 3.991 | Odds ratio 3.29 | Odds ratio 4.619 |
| | Std. Err. 1.96 | Std. Err. 2.02 | Std. Err. 3.55 |
| | *z* 2.16 | *z* 1.94 | *z* 1.99 |
| | *P* .05 | *P* .04 | *P* .04 |
| | 95% CI 0.98-9.44 | 95% CI 0.98-10.96 | 95% CI 1.02-20.86 |
| **Histologic Type** | Odds ratio 1.203 | Odds ratio 1.051 | Odds ratio 0.992 |
| | Std. Err. 0.76 | Std. Err. 0.41 | Std. Err. 0.49 |
| | *z* 0.29 | *z* 0.13 | *z* −0.02 |
| | *P* .77 | *P* .89 | *P* .98 |
| | 95% CI 0.34-4.21 | 95% CI 0.49-2.24 | 95% CI 0.37-2.62 |
| **Chemotherapy** | Odds ratio 0.559 | Odds ratio 1.223 | Odds ratio 1.126 |
| | Std. Err. 0.33 | Std. Err. 0.41 | Std. Err. 0.45 |
| | *z* −0.97 | *z* 0.59 | *z* 0.30 |
| | *P* 0.33 | *P* .55 | *P* .76 |
| | 95% CI 0.17-1.81 | 95% CI 0.62-2.38 | 95% CI 0.51-2.47 |
| **Radiation Dose** | Odds ratio 1.023 | Odds ratio 1.008 | Odds ratio 1.011 |
| | Std. Err. 0.07 | Std. Err. 0.02 | Std. Err. 0.03 |
| | *z* 0.32 | *z* 0.33 | *z* 0.35 |
| | *P* .75 | *P* .73 | *P* .72 |
| | 95% CI 0.88-1.18 | 95% CI 0.96-1.05 | 95% CI 0.95-1.07 |


**This retrospective study evaluates adjuvant thoracic radiotherapy in pathologic N2 non–small-cell lung cancer (NSCLC).**

**Sixty-six patients received postoperative radiotherapy (PORT). Actuarial local control was 80% at 12 months, 77.2% at both 24 and 36 months, and 72.1% at 60 months. Overall survival at 12 months and 60 months was 77% and 37%, respectively.**

**The number of metastatic lymph nodes was a prognostic factor for local control and survival.**

**Background:** Adjuvant radiotherapy in non–small-cell lung cancer (NSCLC) is still controversial. The purpose of this retrospective study was to evaluate the role of postoperative radiotherapy (PORT) in terms of local control and survival in pathologic N2 NSCLC. **Patients and Methods:** From January 2003 to December 2008, 66 patients with pathologic N2 NSCLC received PORT. Mediastinal lymph node metastases were classified into single (12 patients) or multiple (54 patients) stations. All patients received conformal radiation therapy, with a median total dose of 50.4 Gy. Target volumes included the bronchial stump, ipsilateral hilum, all pathologically involved lymph node regions, and all the lymph nodes between 2 noncontiguous pathologic nodal stations. The pattern of failure was considered as locoregional or systemic, or a combination of both. Locoregional failure was defined as in field or out of field. **Results:** Median follow-up time was 34.9 months (range 3.5-62.8 months). Local control was 80% at 12 months, 77.2% at both 24 and 36 months, and 72.1% at 60 months. The pattern of failure was locoregional in 3 patients (1 out of field and 2 in field) and systemic in 25 patients, with 12 patients presenting both locoregional and distant disease. Overall survival at 12, 36, and 60 months was 77%, 44%, and 37%, respectively. Median survival time was 34 months. The number of pathologically involved lymph node stations was a prognostic factor for local control ($P = .05$), cancer-specific survival (CSS) ($P = .04$), and disease-free survival (DFS) ($P = .04$). **Conclusion:** Despite the limitations of the present study, mainly represented by its retrospective nature, our data support the role of PORT in terms of locoregional control and overall survival benefit; the number of involved mediastinal lymph nodes represents a significant prognostic factor in patients with pathologic N2 NSCLC.


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Mantovani et al. Clin Lung Cancer. 2013

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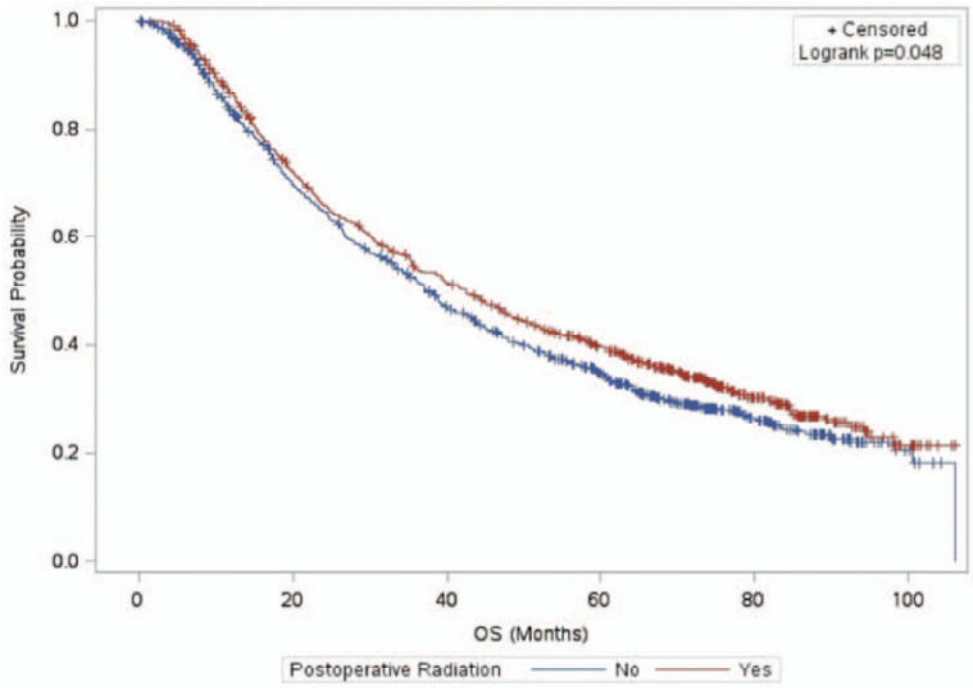
# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

## Postoperative Radiotherapy is Associated with Better Survival in Non–Small Cell Lung Cancer with Involved N2 Lymph Nodes

### *Results of an Analysis of the National Cancer Data Base*




**Introduction:** Use of postoperative radiotherapy (PORT) in non–small-cell lung cancer remains controversial. Limited data indicate that PORT may benefit patients with involved N2 nodes. This study evaluates this hypothesis in a large retrospective cohort treated with chemotherapy and contemporary radiation techniques.

**Methods:** The National Cancer Data Base was queried for patients diagnosed 2004–2006 with resected non–small-cell lung cancer and pathologically involved N2 (pN2) nodes also treated with chemotherapy. Multivariable Cox proportional hazards model was used to assess factors associated with overall survival (OS). Inverse probability of treatment weighting (IPTW) using the propensity score was used to reduce selection bias. OS was compared between patients treated with versus without PORT using the adjusted Kaplan–Meier estimator and weighted log-rank test based on IPTW.

**Results:** Two thousand and one hundred and fifteen patients were eligible for analysis. 918 (43.4%) received PORT, 1197 (56.6%) did not. PORT was associated with better OS (median survival time 42 months with PORT versus 38 months without, $p = 0.048$). This effect was significant in multivariable and IPTW Cox models (hazard ratio: 0.87, 95% confidence interval: 0.78–0.98, $p = 0.026$, and hazard ratio: 0.89, 95% confidence interval: 0.79–1.00, $p = 0.046$, respectively). No interaction was seen between the effects of PORT and number of involved lymph nodes ($p = 0.615$).

**Conclusions:** PORT was associated with better survival for patients with pN2 nodes also treated with chemotherapy. No interaction was seen between benefit of PORT and number of involved nodes. These findings reinforce the benefit of PORT for N2 disease in modern practice using the largest, most recent cohort of chemotherapy-treated pN2 patients to date.

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# ADVANCED STAGE LUNG NSCLC:

## *Neoadjuvant vs adjuvant*

2. Timing with Surgery: neoadjuvant versus **adjuvant**

### Final remark

**4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high** (Grade 2C).

*Remark*: Adjuvant postoperative radiotherapy reduces the incidence of local recurrence, but it is unclear whether it improves survival.

**4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested** (Grade 2C).

*Remark:* Incomplete resection (R1,2) does not appear to confer a survival benefit over no resection.



CHEST 2013; 143(5)(Suppl):e314S–e340S

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# LUNG OLIGOMETASTASES:
## .. THE ROLE OF SABR

The Oncologist

Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

Filippo Alongi,[a] Stefano Arcangeli,[a] Andrea Riccardo Filippi,[b] Umberto Ricardi,[b] Marta Scorsetti[a]

Radiation Oncology

H. Badakhshi · A. Grün · C. Stromberger · V. Budach · D. Boehmer
Department for Radiation Oncology, Charité University Medicine, Berlin

Oligometastases: the new paradigm and options for radiotherapy

A critical review

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Seminars in RADIATION ONCOLOGY

To SABR or Not to SABR? Indications and Contraindications for Stereotactic Ablative Radiotherapy in the Treatment of Early-Stage, Oligometastatic, or Oligoprogressive Non–Small Cell Lung Cancer

David Benjamin Shultz, MD, PhD,[*,†] Maximilian Diehn, MD, PhD,[*,†,‡] and Billy W. Loo Jr. MD. PhD[*,†]

- The concept of Oligomestastatic disease was proposed nearly 20 years ago.
- SABR is quite effective than surgery for controlling pulmunary metastases

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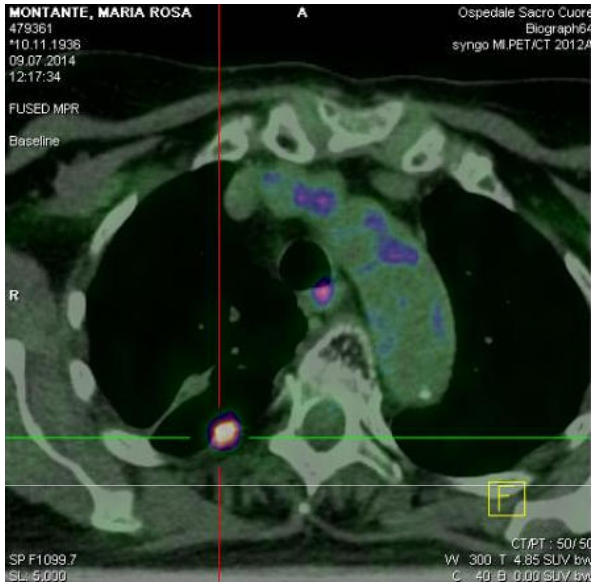
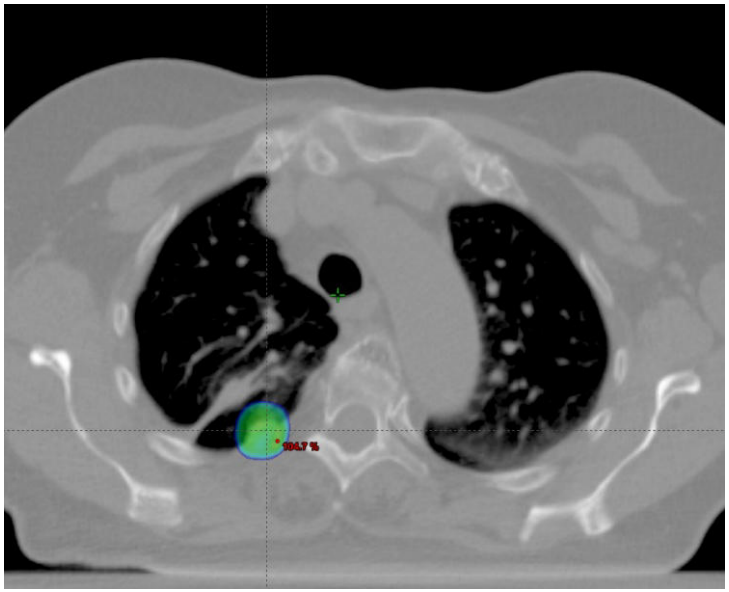
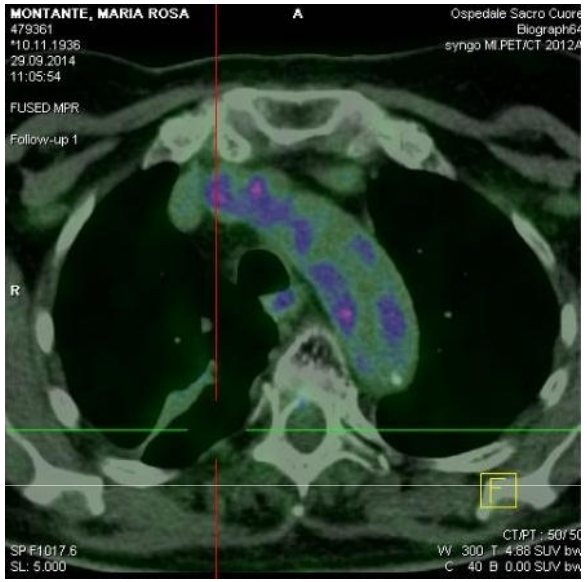
# STEREOTACTIC BODY RT(SBRT):
## LUNG OLIGOMTS

TRUEBEAM treatment for colon lung
Peripheric metastasis






PET before SBRT

48 Gy/4 fr. with Truebeam

CR @ 60 days

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# SBRT and… "OLIGOPROGRESSIVE"

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Seminars in RADIATION ONCOLOGY

Semin Radiat Oncol 25:78-86 © 2015

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## To SABR or Not to SABR? Indications and Contraindications for Stereotactic Ablative Radiotherapy in the Treatment of Early-Stage, Oligometastatic, or Oligoprogressive Non–Small Cell Lung Cancer

David Benjamin Shultz, MD, PhD,[*,†] Maximilian Diehn, MD, PhD,[*,†,‡] and Billy W. Loo Jr, MD, PhD[*,†]

Strahlenther Onkol (2015) 191:453–455
DOI 10.1007/s00066-015-0826-2

LITERATUR KOMMENTIERT

## Oligoprogression

**Eine innovative Indikation für die Körperstereotaxie bei metastasierten Tumorsituationen**

**Matthias Guckenberger**

Online publiziert: 5. März 2015


## Can SABR Be Used to Treat Oligoprogressive Disease Occurring in the Setting of Targeted Therapy?

Patients with NSCLC who were treated with targeted agents eventually develop progression owing to the emergence of drug-resistant clones. Because most cancer may retain a drug-sensitive genotype, it has been hypothesized that, in this clinical scenario, patients should be maintained on the same targeted therapy and that the resistant clones, which are phenotypically distinguished as oligoprogressive tumors, should be treated with surgery, CFRT, or SABR. Studies in which SRS or SABR was used to treat patients with oligoprogressive NSCLC that was either intracranial only[113] or intracranial and systemic [114,115] while being maintained on a targeted agent have been reported. Weickhardt et al reported their retrospective experience of using SABR, CFRT, and surgery with the goal of prolonging the effectiveness of targeted therapy in patients with NSCLC. Overall, 25 patients with *ALK* rearranged or *EGFR* mutation-driven tumors were included in the study, and sites of oligoprogression were classified as being

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# CONCLUSIONS AND TAKE HOME MESSAGE

IIIA-B:

- Radiochemotherapy is the standard
- New technology allow us to perform with safety RT-CT
- Adjuvant approach is to discuss in case of N2

Stage IV :

- SABR for oligometastatic and oligoprogressive disease is an open issue..

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# ADVANCED STAGE LUNG NSCLC:
## CONCLUSIONS

# THANK YOU

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