MADRID 2014 ESMO congress

Challenging cases of oligometastatic NSCLC

A patient with a right upper lobe peripherally located T1b adenocarcinoma with a bone metastasis in the left rib 9 and in dorsal vertebra 4

U. Ricardi

AZIENDA OSPEDALIERO - UNIVERSITARIA
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Nothing to disclose

Challenging cases of oligometastatic NSCLC

A patient with a **left lower lobe** peripherally located T1b adenocarcinoma with a bone metastasis in the **right rib 4** and in **dorsal vertebra 11**

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Clinical History

M.M.

- Male, 73 yo
- PS 0 ECOG
- Former smoker
- Comorbidities: DM II, hypertension, CAD
- December 2010: persistent coughing and right chest wall pain
- Chest X Ray: opacity in left lower lobe
- Lab: no suspicious findings (CEA, NSE : negative)

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Clinical History

- **Total body CT scan (January 2011)**

  ✓ Left lower lobe parenchimal tumor (diam 30 mm); no other pathologic findings

- **CT-PET scan (January 2011)**

  ✓ Pathologic uptake in lower lobe lesion (SUV 2.9), in right rib 4 (SUV 3.3) and in D11 (SUV 4.2)

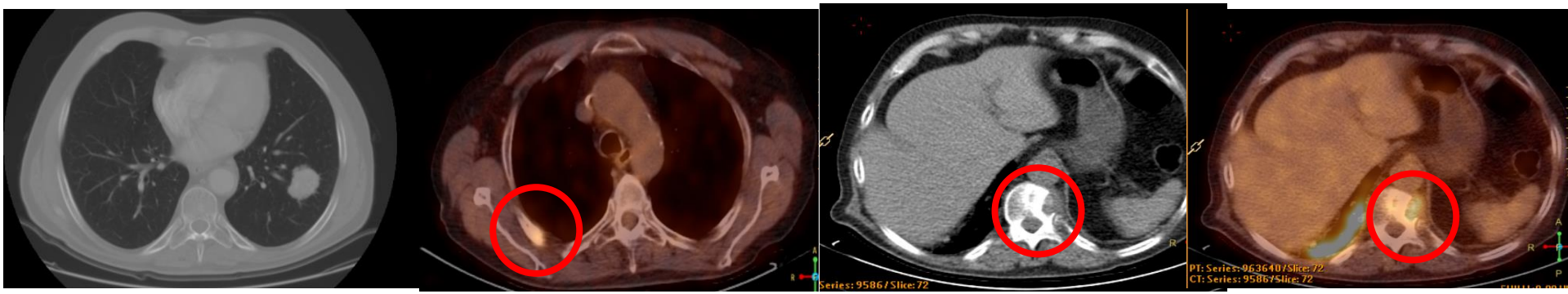
- **Chest MR scan and bone scintigraphy:**

  ✓ both findings compatible with bone mets

Male 72 yrs, PS 0, ex-smoker

FNAB left lower lobe T and rib lesion: EGFR-Wt ALK-negative adenocarcinoma

Stage IV, cT1b N0 M1b (bone) Adequate PFT



1. chemotherapy only
2. chemotherapy → thoracic surgery → bone RT
3. thoracic surgery → chemotherapy ± RT
4. SBRT (T and oligoM) → chemotherapy

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Chemotherapy

- Carboplatin and Pemetrexed for 3 cycles (completed at beginning of April 2011)
- Moderate toxicity
- At restaging: SD

Surgery

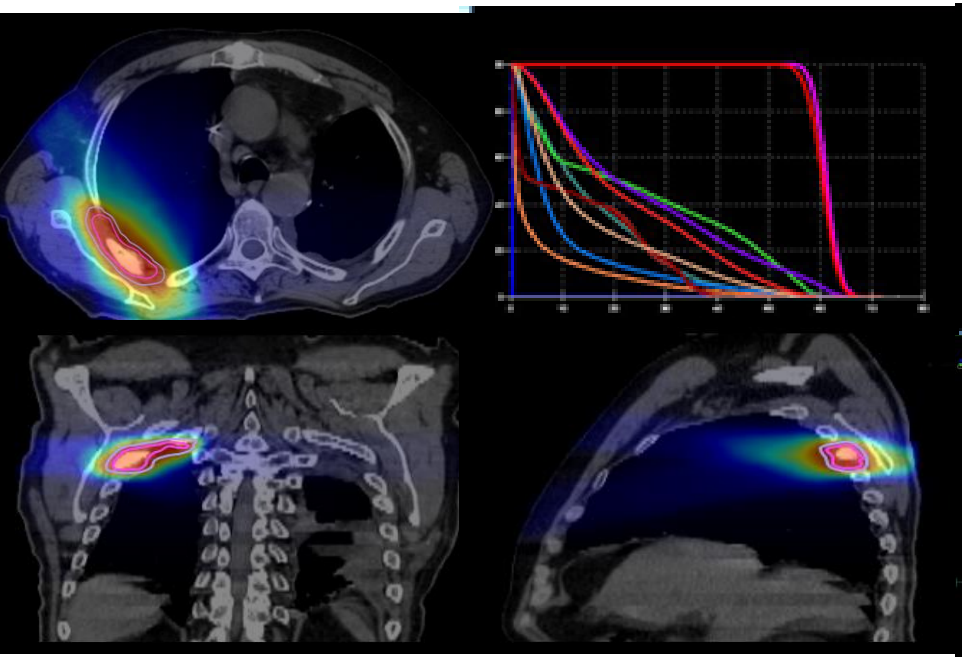
- Lobectomy and systematic lymphadenectomy (May, 2011)

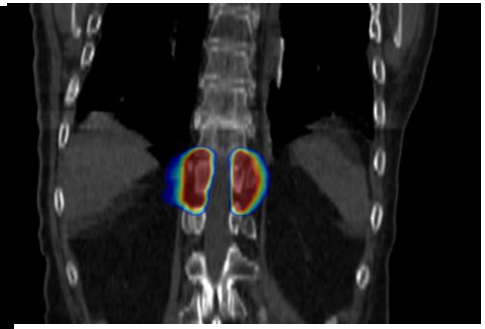
- Adenocarcinoma, G2, pT1bN1 (1 lobar node)

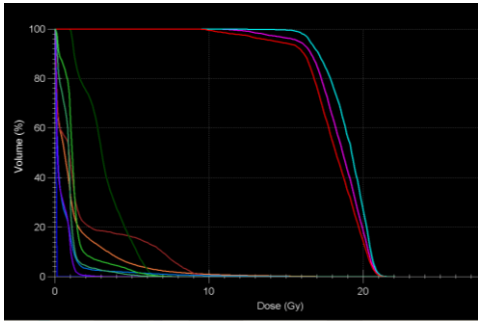
Radiation treatment (July, 2011)

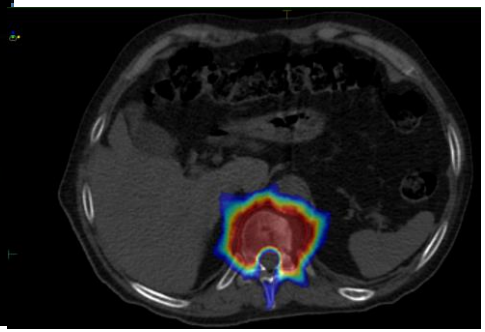
30 Gy/5 fractions

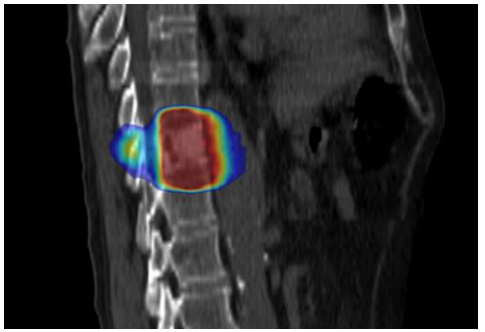
Single fraction SBRT: 16 Gy



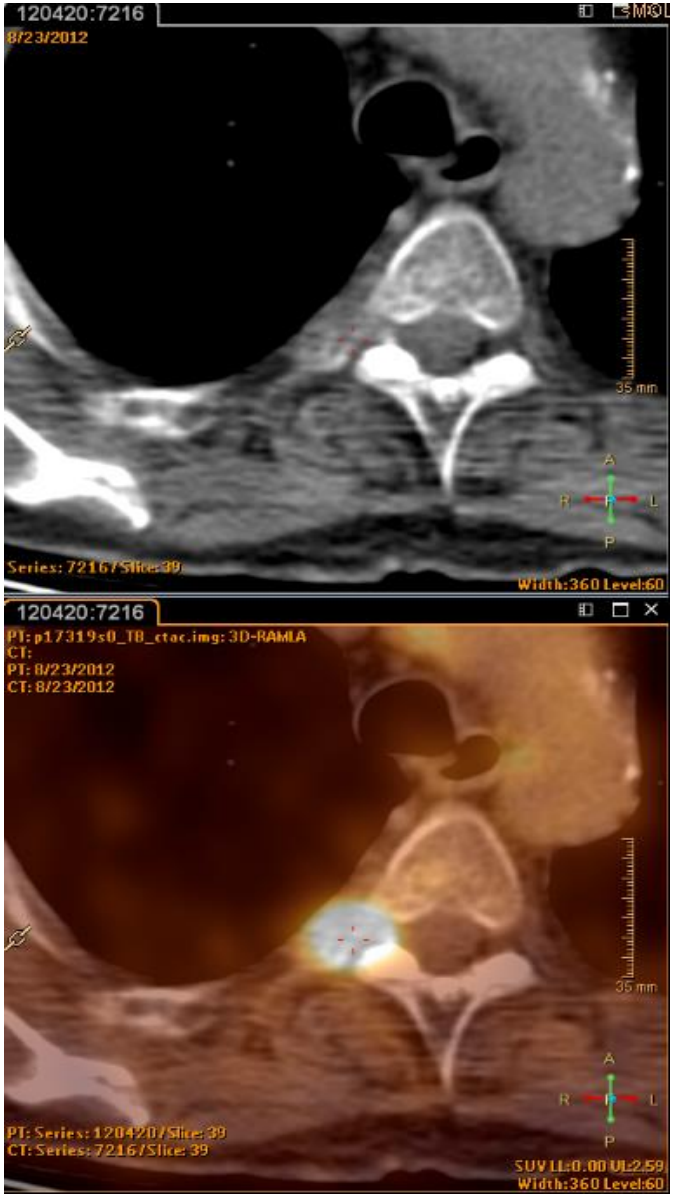


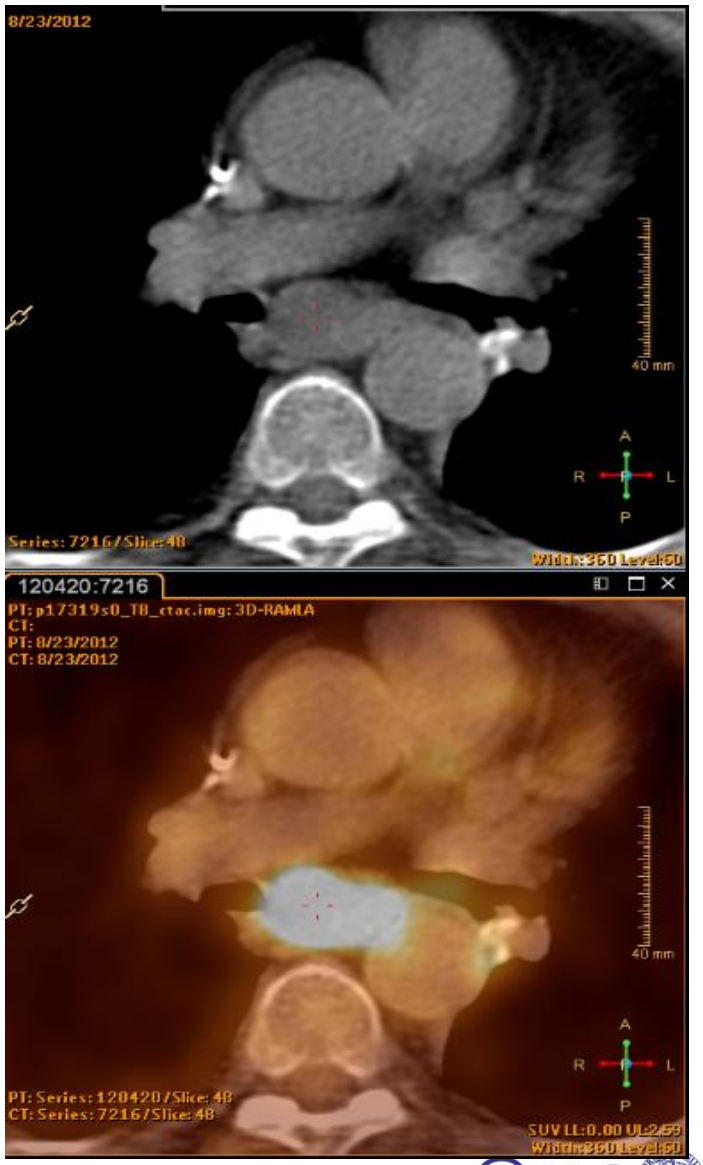






PET-CT scan (August 2012)





Therapeutic proposal

Radiotherapy (on both mediastinal disease and paraspinal solitary met → local pain)

January 2014: pathological fracture of the left femur → osteosynthesis and adjuvant conventional RT

September, 2014

- WHO performance status: 1
- SD at mediastinal level
- Good control of bony lesions pain (VAS: 3 vs VAS: 8-9)

Challenging cases of oligometastatic NSCLC

A patient with a **left lower lobe** peripherally located T1b adenocarcinoma with a bone metastasis in the **right rib 4** and in **dorsal vertebra 11**

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The Oligometastatic State

- Do patients with limited metastases exist?

Terminology and definition

Editorial 1995 : proposal of a new clinical concept :

“Oligometastases”

Intermediate biologic state of restricted metastatic capacity

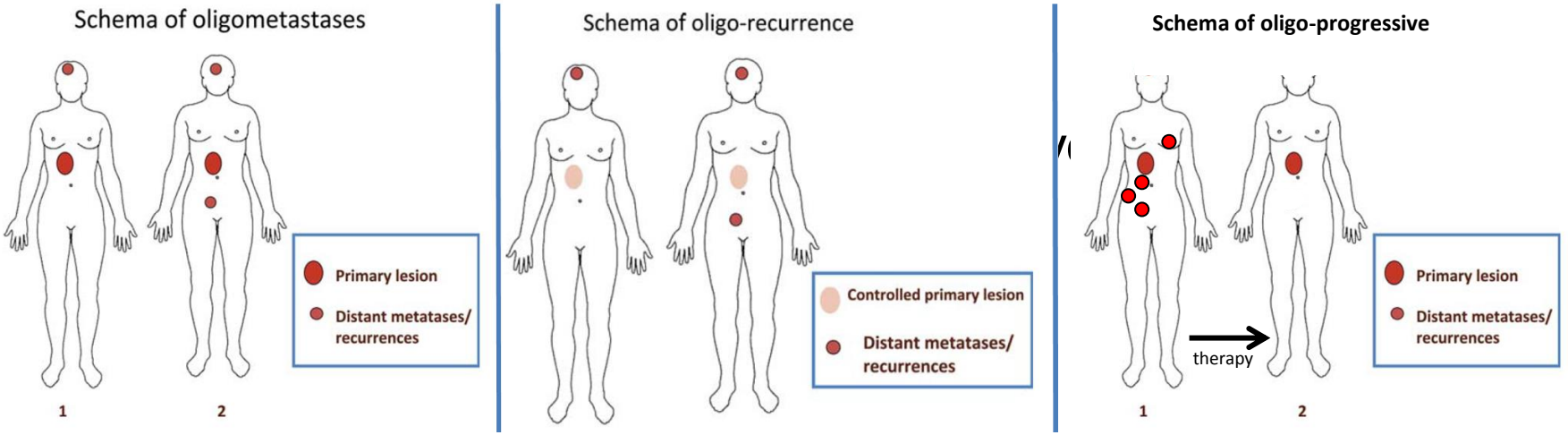
Limited number and organ sites of metastases

Transitional state to dissemination

Weichselbaum & Hellmann. J Clin Oncol 1995;13:8.
Weichselbaum & Hellmann. Nat Rev Clin Oncol 2011;8:378.

Distinct cohorts of oligometastatic disease

"oligometastases" = diagnosed with oligometastatic disease
"oligorecurrence" = relapsed oligometastatic disease
"oligoprogressive" = oligometastatic disease after cytoreductive therapy



→ These cohorts have probably different prognoses

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The Concept of Oligometastases

- **The oligometastatic hypothesis**

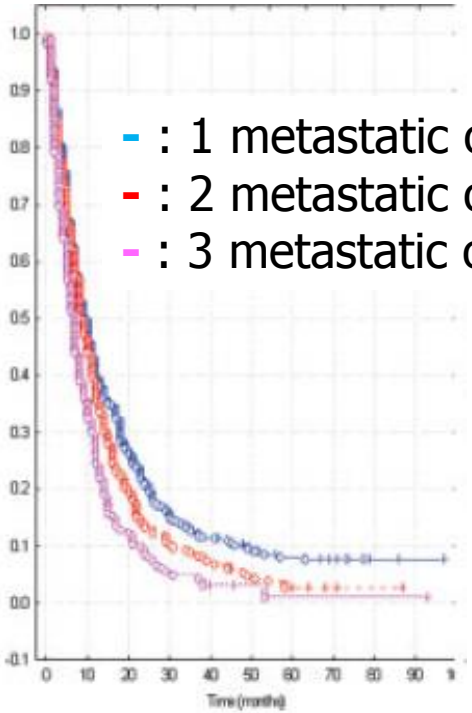
- **“cancer is a biologic spectrum…..with many intermediate states”**
- **“metastases can be limited in number and location and not be associated with widespread metastatic disease”**
- **“An attractive consequence of the oligometastatic state is that some patients should be amenable to a curative therapeutic strategy”**

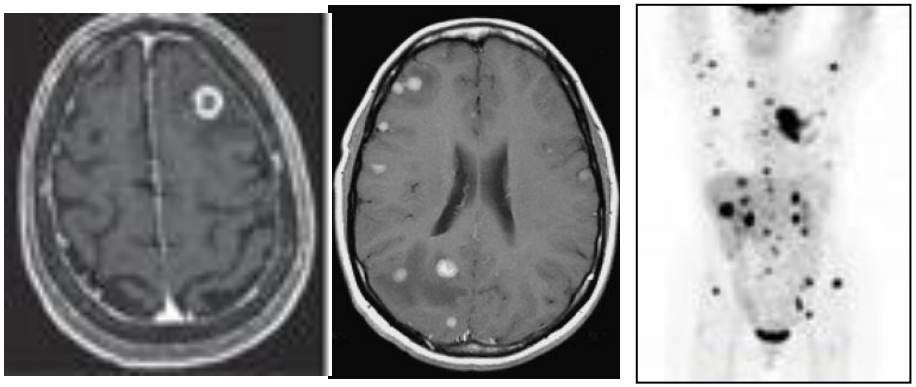
Terminology and definition

Editorial 1995 : proposal of a new clinical concept :

“Oligometastases”

→ Clinical evidence suggesting existence of oligometastases





- Oligometastatic state: limited number of metastases (usually ≤ 5), all amenable to radical local therapies

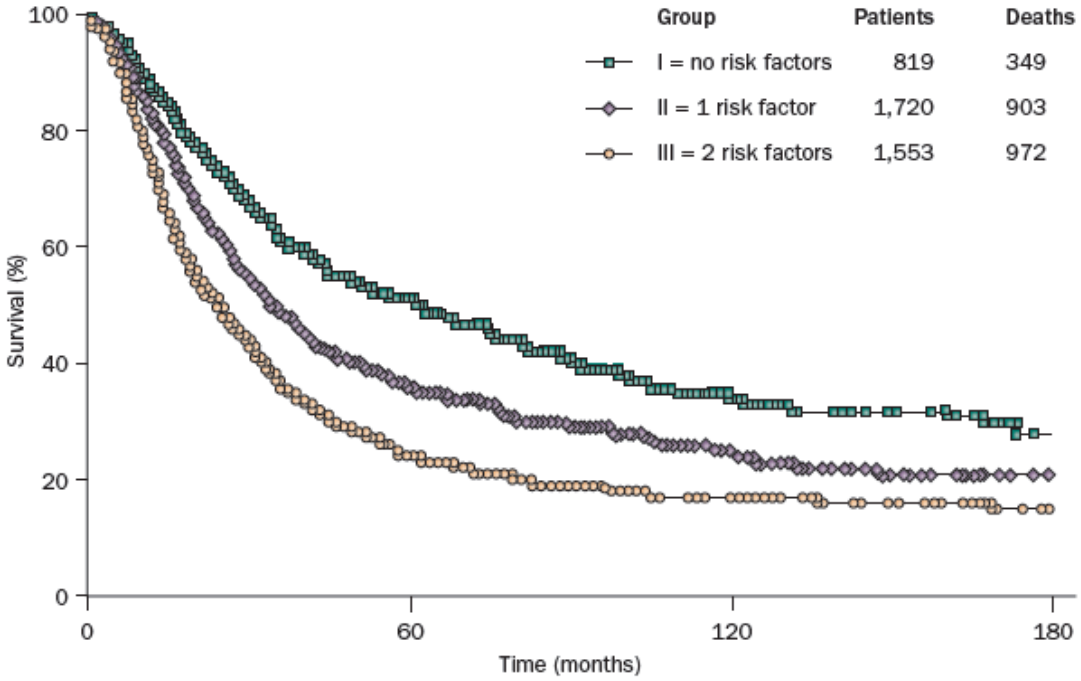
Oh et al. Cancer 2009;115:2930

The Oligometastatic State

- Do patients with limited metastatic disease behave differently than those with more widespread metastases?

LONG-TERM RESULTS OF LUNG METASTASECTOMY: PROGNOSTIC ANALYSES BASED ON 5206 CASES

International Registry of Lung Metastases
Ugo Pastorino, MD



MEDIAN SURVIVAL TIME:

- Group I: 61 mo
- Group II: 34 mo
- Group III: 24 mo

RISK FACTORS:

- Disease-Free Interval from primary tumor to mts < 36 months
- Multiple metastases

The Journal of Thoracic and Cardiovascular Surgery
January 1997

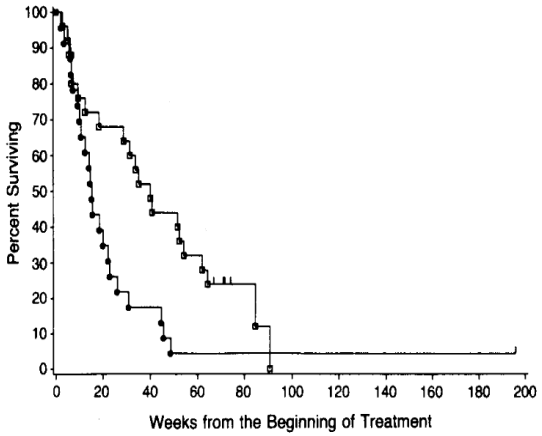
The Oligometastatic State

- Has the aggressive treatment of metastases already improved outcomes?

Level 1 Evidence

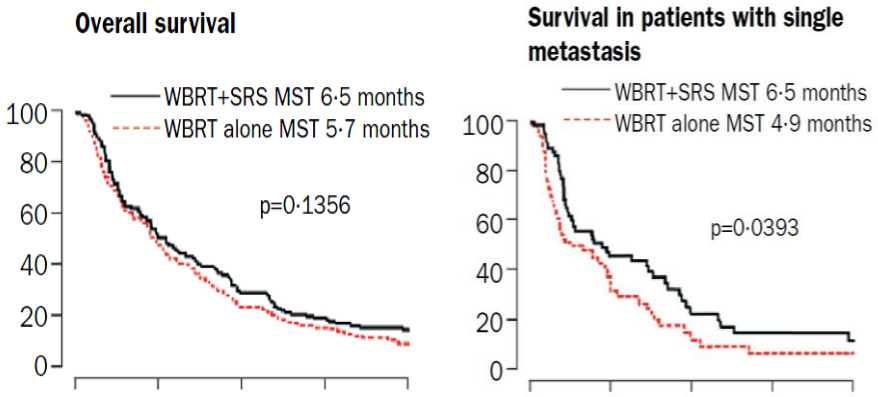
A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

Roy A. Patchell, M.D., Phillip A. Tibbs, M.D., John W. Walsh, M.D., Robert J. Dempsey, M.D., Yosh Maruyama, M.D., Richard J. Kryscio, Ph.D., William R. Markesbery, M.D., John S. Macdonald, M.D., and Byron Young, M.D.

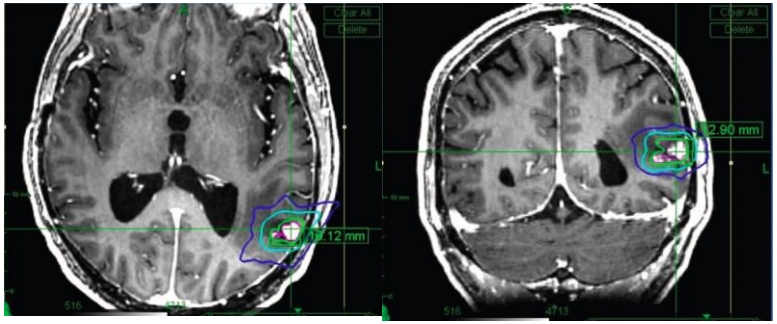


- **Patchell et al. NEJM 1990**

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial



- **Andrews et al. Lancet 2004**



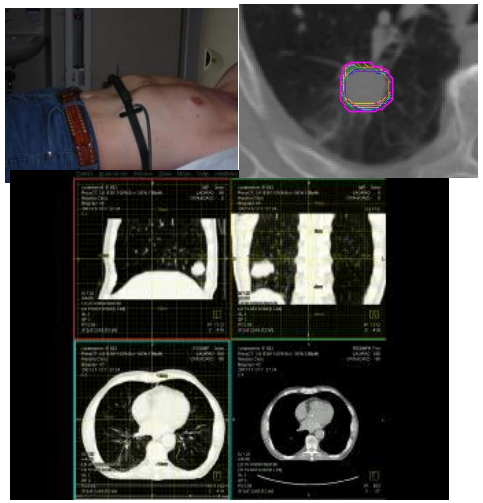
The Oligometastatic State

- Radical irradiation for extracranial oligometastases

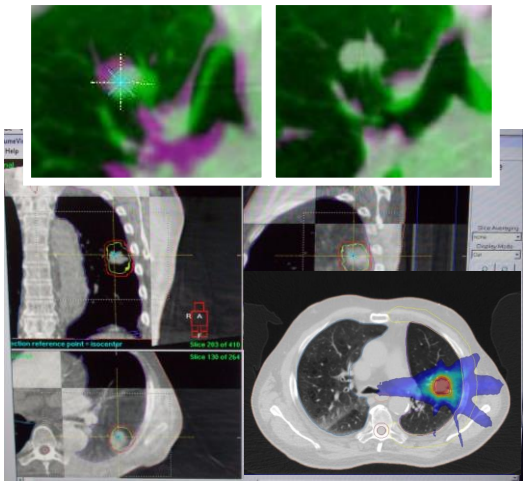
SBRT

A technique for delivering external beam radiotherapy

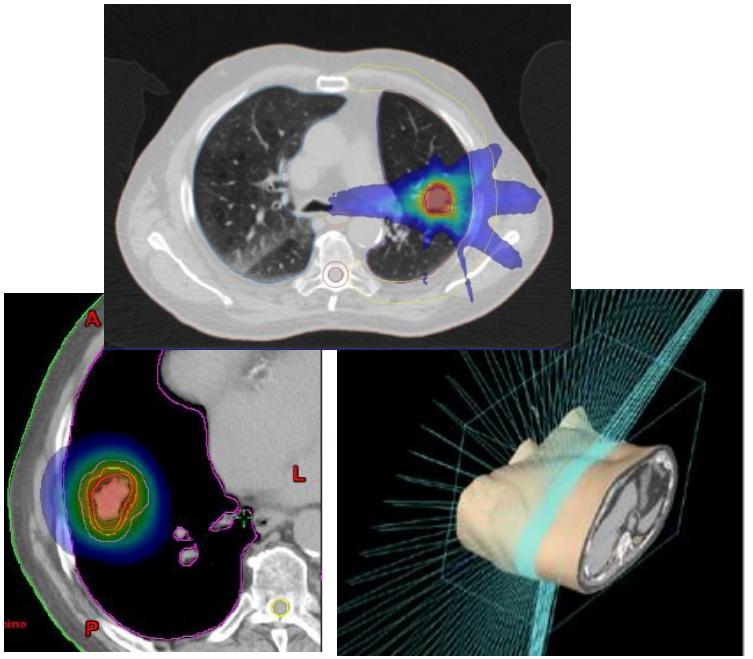
i. with a high degree of accuracy to an extra-cranial target,
ii. using high doses of irradiation,
iii. in 1-8 treatment fractions.



4-D imaging

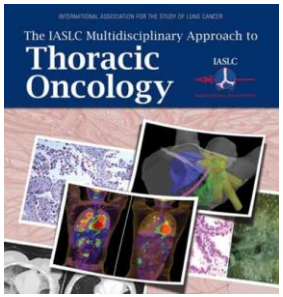


Sophisticated plans
CT scan on treatment couch



Delivery in <4 mins (FFF)

S. Senan, M. Guckemberger, U. Ricardi
Stage I NSCLC and oligometastatic disease
The IASLC Multidisciplinary approach to Thoracic Oncology, 2014



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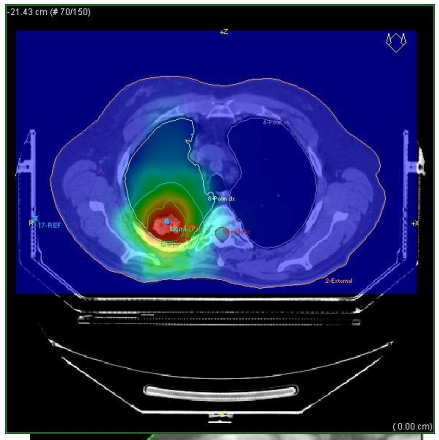
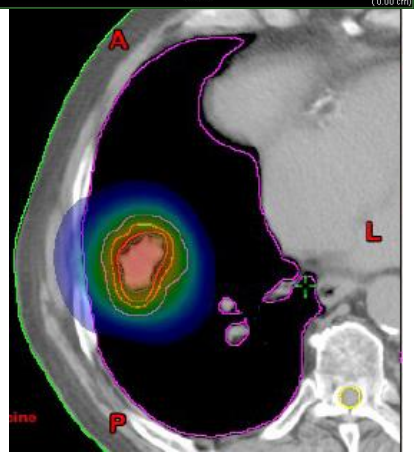
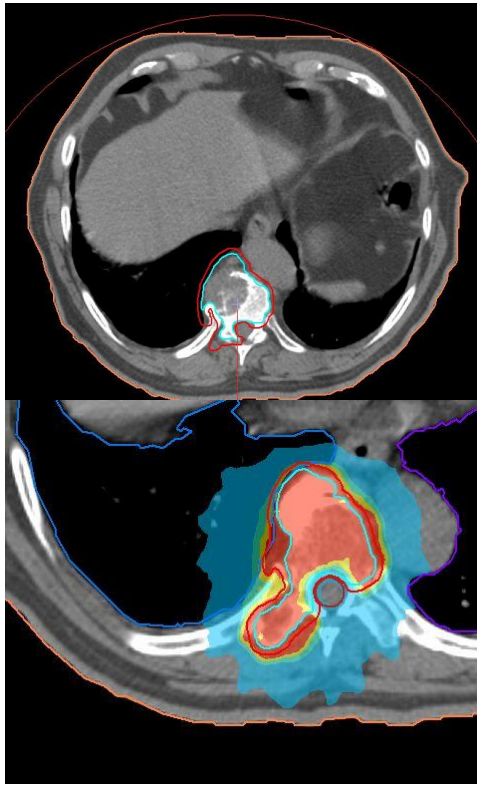
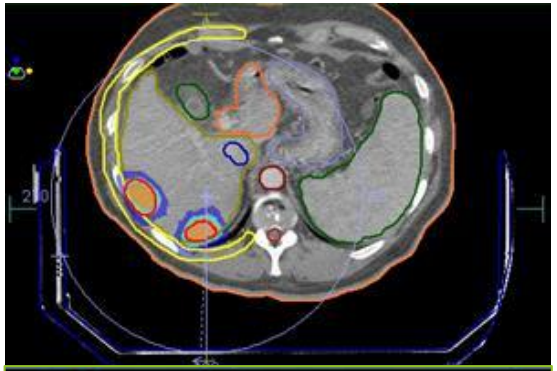
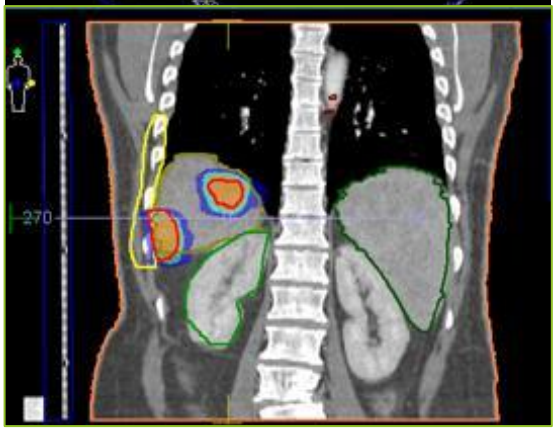


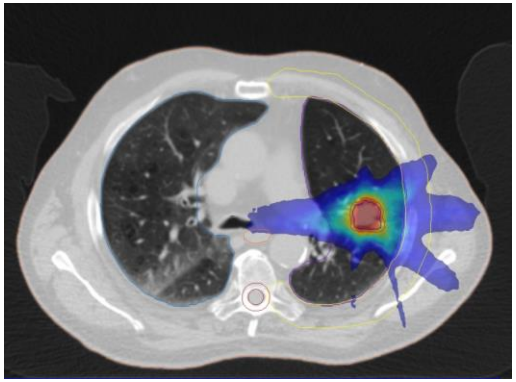


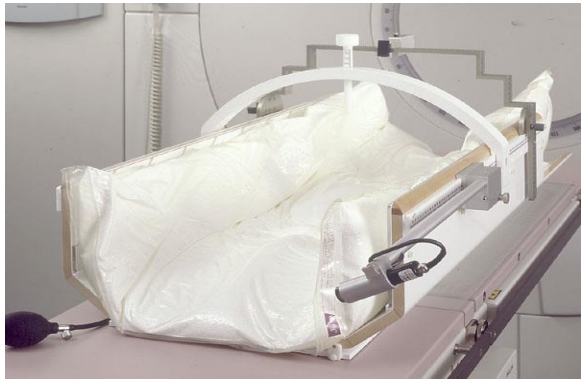


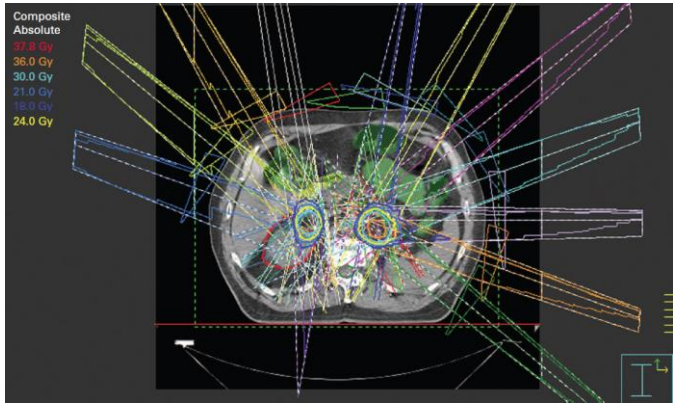




Stereotactic Body Radiation Therapy (SBRT)







Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD, Andrea Riccardo Filippi, MD,† Juliette Thariat, MD,‡ Francoise Mornex, MD, PhD,‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD†*

TABLE 1. Clinical Trials of Stereotactic Ablative Radiotherapy for Pulmonary Oligometastatic Disease

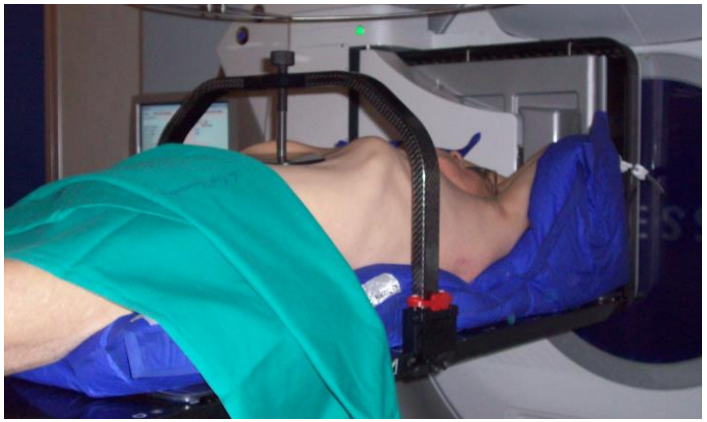
Reference	No. of Patients	No. of Targets	Radiation Dose	Median Follow-Up (Months)	Outcomes
Fractionated/Single Fraction SABR					
Onimaru et al.[27]	20	32	48 Gy/8 fx, 60 Gy/8 fx	18	48% 2-yr OS, 69.6% 3-yr LC for 48 Gy, 100% 3-yr LC for 60 Gy
Yoon et al.[26]	53	80	30 Gy/3 fx, 40 Gy/4 fx, 48 Gy/4 fx	14	70% LC for 30 Gy, 77% for 40 Gy, 100% LC for 48 Gy, 51% all 2-yr OS
Okunieff et al.[28]	50	125	50 Gy/10 fx, 48 Gy/6 fx, 57 Gy/3 fx	18.7	91% 3-yr LC, 50% 2-yr OS
Norihisa et al.[18]	34	43	48 Gy/4 fx, 60 Gy/5 fx, at isocenter	27	90% 2-yr LC, 84% 2-yr OS
Brown et al.[25]	35	69	5 Gy/1 fx to 60 Gy/4 fx	18	77% crude LC, 72.5% 2-yr OS
Rusthoven et al.[12]	38	63	60 Gy/3 fx at 80%	15.4	96% 2-yr LC, 39% 2-yr OS
Wulf et al.[24]	41	51	30 Gy/3 fx, 36 Gy/3 fx, 26 Gy/1 fx at 100%	13	80% 1-yr LC, 33% 2-yr OS
Ricardi et al.[23]	61	77	45 Gy/3 fx, 26 Gy/1 fx at 80%	20.4	89% 2-yr LC, 66.5% 2-yr OS
Single Fraction SABR Only					
Hof et al.[30]	61	71	12 to 30 Gy at isocenter	14	65.1% 2-yr OS
Filippi et al.[29]	67	90	26 Gy at 80%	24	88.1% 2-yr LC, 70.5% 2-yr OS

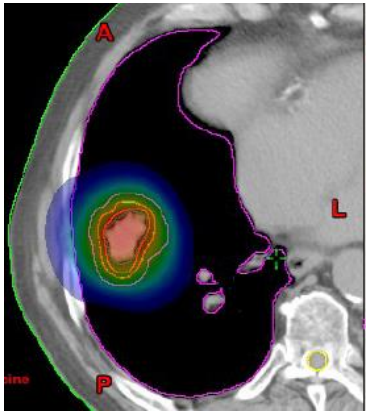
(*J Thorac Oncol.* 2014;XX: 00–00)

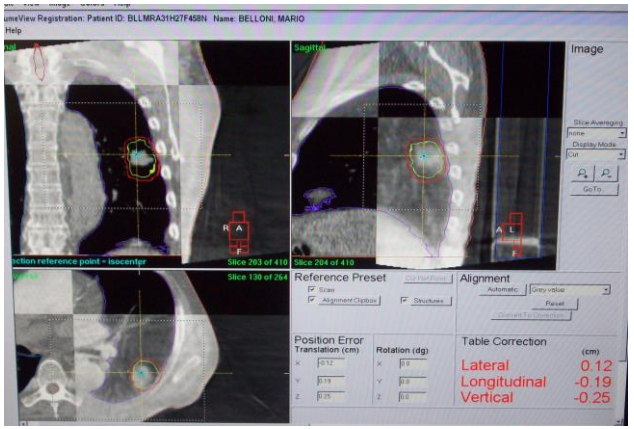
SBRT in the Oligometastatic State

- No randomized data are available
- A proper comparison between the published studies is hampered mainly by the different selection criteria and the widely variable fractionation schedules
- When treating metastatic patients (even if "oligometastatic"), selection criteria are a pivotal issue
- In general, clinical indications are the same as those for metastasectomy, but without the limits regarding patients unfit for surgery and invasiveness

Patient management







- Outpatient
- 20-60 minutes per treatment
- Entire course Rx in 1-2 weeks
- 3-8 treatments qd
- No sedation or anesthesia (painless)
- Immediate return to activities

The Oligometastatic State

- How has radical irradiation been integrated into the treatment of specific diseases?

- Is there an Oligometastatic State in NSCLC?

Department of Oncology
University of Turin

Is there an Oligometastatic State in NSCLC?

Table 1: Selected series for the comprehensive treatment of metastatic NSCLC.

Study	*N*	Metastatic sites	Treatments	1-year PFS	5-year OS
University of Maryland [23]	72	Brain (metachronous)	SRS		13.2%
University of Maryland [24]	42	Brain (synchronous)	SRS, TS, RT, CRT, HIGRT		21%
Hopital Louis Pradel Hospices Civils de Lyon, Lyonnce [25]	51	Brain (synchronous)	BS, TS, RT, CRT		42% (BS + others) versus 5% (BS only)*
University of Rochester [26]	38	Multisite, 1–8 metastases	HIGRT		14%
Rush University Medical Center [27]	23	Multi-site, 1-2 metastases	TS, RT, HIGRT		22%
University of Chicago [28]	25	Multi-site, 1–5 metastases	HIGRT (3–10 fx)	28%	53% (18 mo)
Maastricht University Medical Center [29]	39	Brain, bone, adrenal	TS, SRS, RT, HIGRT		24%*

*2 yr estimates; SRS: stereotactic radiosurgery; BS: brain surgery; TS: thoracic Surgery; RT: radiotherapy; CRT: chemoradiotherapy; HIGRT: hypofractionated image-guided radiotherapy.

But, are these favourable outcomes due to aggressive therapy, the underlying nature of these diseases, or both?

Patel et al, Pulmonary Medicine, 2012

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

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

n=39 pts

- Phase II single-arm prospective trial
- < 5 synchronous oligomts
- All tumor sites amenable for radical treatment (surgery or RT)
- Systemic treatment not mandatory (but 95% chemo-beam)
- Not size limitations for primary tumor or mts

- PRIMARY ENDPOINT: OS @ 2 and 3 ys

Local stage (ignoring M1 status)	
I	4 (10.3%)
II	6 (15.4%)
IIIA	9 (23.1%)
IIIB	20 (51.3%)
Localization metastasis	
Adrenal gland	4 (10.3%)
Bone	7 (17.9%)
Brain	17 (43.9%)
Gastro-hepatic ligament	1 (2.6%)
Liver	1 (2.6%)
Lung	1 (2.6%)
Lymph node	2 (5.1%)
Muscle	2 (5.1%)
Ovary	1 (2.6%)
Pleura	3 (7.7%)
Number metastases	
1	34 (87.2%)
2	4 (10.3%)
3	1 (2.6%)

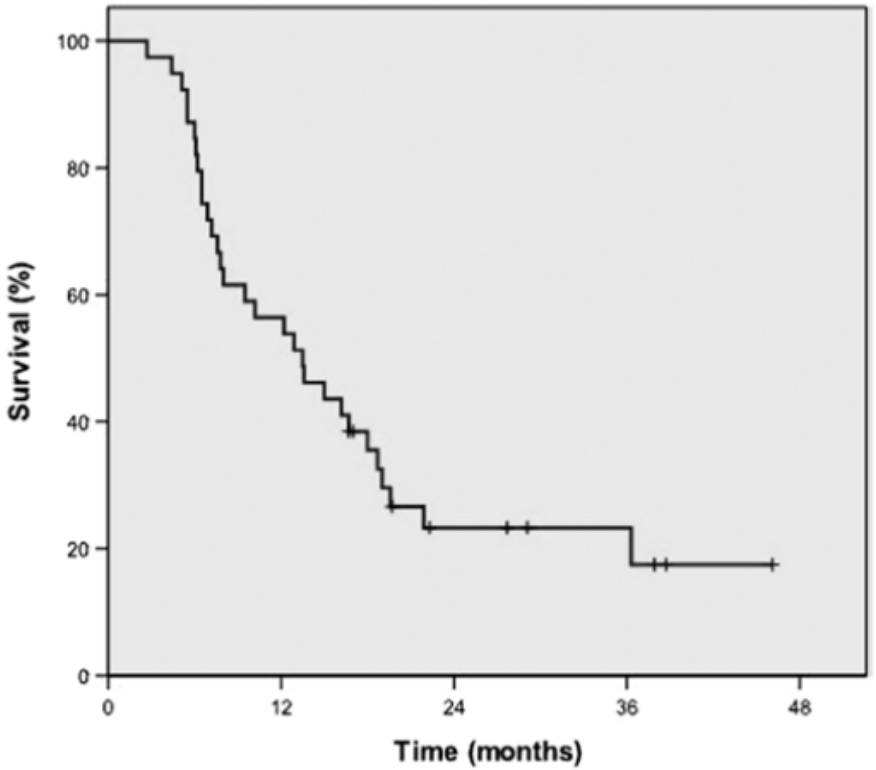
Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

ORIGINAL ARTICLE

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

- Median OS: 13.5 months
- OS @ 2 and 3 ys: 23.3% and 17.5%, respectively
- MST for adrenal locations was 10.2 months, for bone 13.5 months, for brain 13.6 months, for soft tissues 5.5 months



Journal of Thoracic Oncology • Volume 7, Number 10, October 2012

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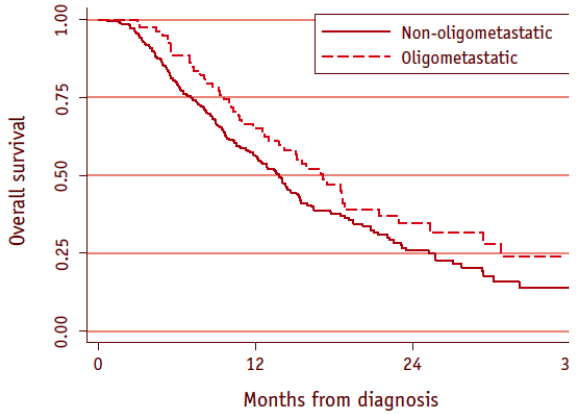
Definitive Primary Therapy in Patients Presenting With Oligometastatic Non-Small Cell Lung Cancer

Ravi B. Parikh



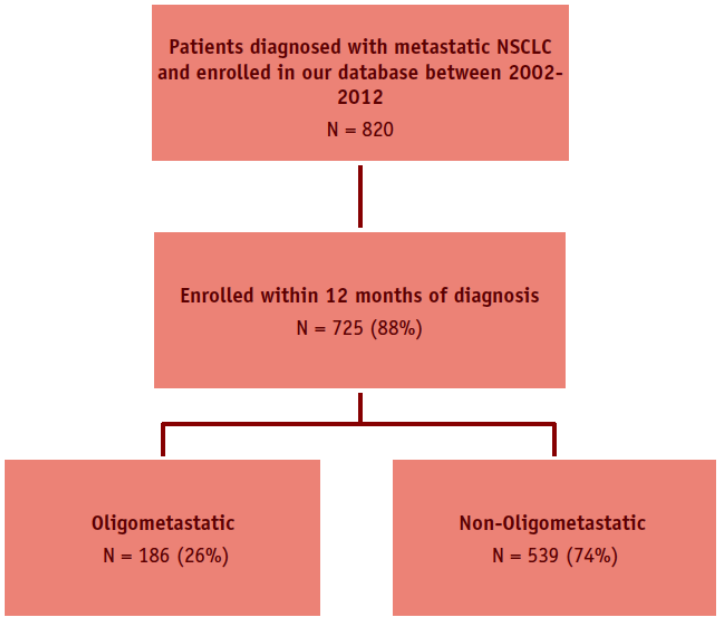


Table 2 Unadjusted association between treatment and overall survival among patients with oligometastatic disease

Treatment	Number of patients (%)	Hazard ratio*	95% CI	*P* Value
No aggressive treatment	101 (54)	1.00	–	–
Yes: to metastatic sites only	32 (17)	0.90	0.57-1.41	.647
Yes: to primary tumor only	16 (9)	0.64	0.33-1.24	.189
Yes: to both metastatic sites and primary tumor	37 (20)	0.59	0.37-0.95	.029

Abbreviation: CI = confidence interval.
* Hazard ratios >1 represent lower overall survival.

ECOG PS ≥ 2, N2-3, squamous histology and >1 metastatic organ involved → significantly associated with worse OS

Site of metastatic disease → not associated with OS

Int J Radiation Oncol Biol Phys, Vol. 89, No. 4, pp. 880–887, 2014

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The Oligometastatic State

- Can irradiation of metastases enhance immunotherapy?
- How do we combine radical irradiation of extracranial oligometastases with systemic therapy?
- How commonly is SBRT being used for the treatment of extracranial oligometastases?
- How do we observe patients treated with radical irradiation of oligometastases?
- **How should patients be selected for radical irradiation of oligometastases?**

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UNIVERSITY OF TURIN

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Published online 18 December 2013

Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival

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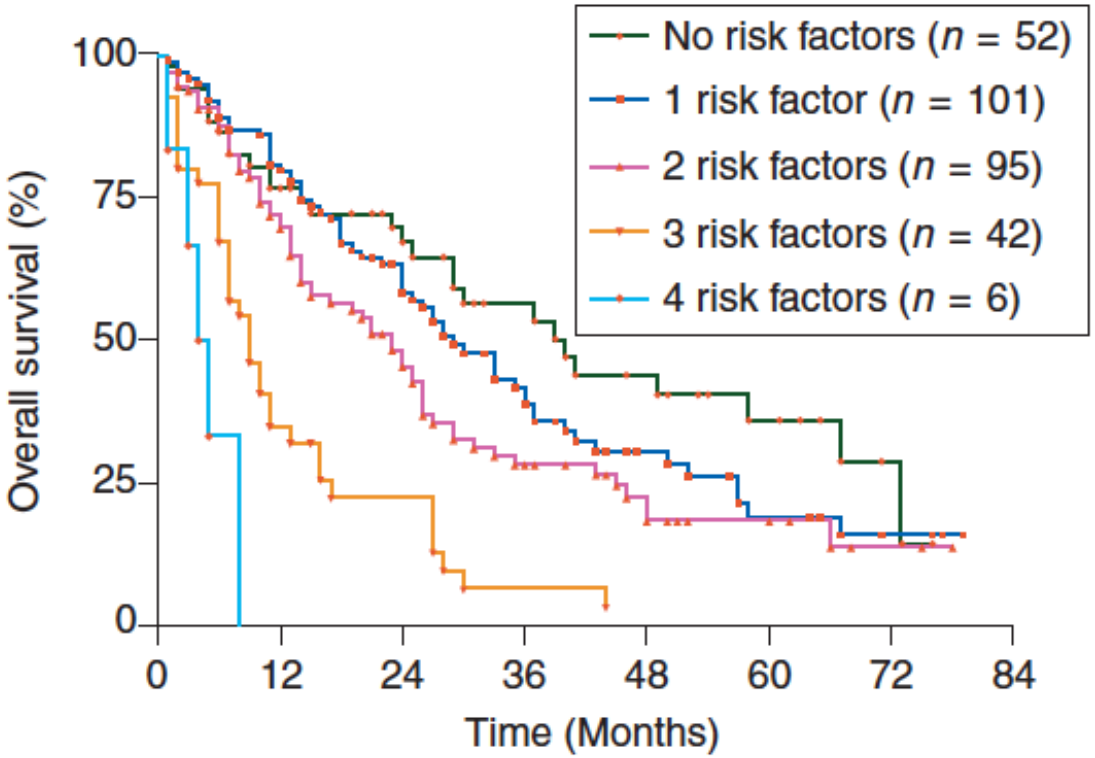

Table 2. Multivariate analysis: prognostic factors for survival

Significant variables	Hazard ratio (95% CI)	*P*-value (cox regression)
Gender		
Female versus male	1.401 (1.046–1.877)	0.024
Histology of primary		
Adenocarcinoma versus nonadenocarcinoma	0.430 (0.309–0.597)	<0.001
Oligometastatic disease		
Metachronous versus synchronous	1.491 (1.113–1.996)	0.007
Oligometastatic site		
Extracranial versus intracranial	1.819 (1.344–2.463)	<0.001
BED ≥75 versus <75 Gy	1.626 (1.058–2.500)	0.023

CI, confidence interval; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; BED, biologically effective dose.

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Can We Identify Long-Term Survivors in Oligometastatic Non-Small Cell Lung Cancer?

An Individual Patient Data Meta-Analysis of Outcomes and Prognostic Factors

Allison B. Ashworth[1], Suresh Senan[2], David A. Palma[1], Marc Riquet[3], Yong Chan Ahn[4], Umberto Ricardi[5], Maria T. Congedo[6], Daniel R. Gomez[7], Gavin M. Wright[8], Giulio Melloni[9], Michael T. Milano[10], Claudio V. Sole[11], Tommaso M. De Pas[12], Dennis L. Carter[13], Andrew J. Warner[1] and *George B. Rodrigues[1]*.

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An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer

Allison B. Ashworth,[1] Suresh Senan,[2] David A. Palma,[1] Marc Riquet,[3] Yong Chan Ahn,[4] Umberto Ricardi,[5] Maria T. Congedo,[6] Daniel R. Gomez,[7] Gavin M. Wright,[8] Giulio Melloni,[9] Michael T. Milano,[10] Claudio V. Sole,[11] Tommaso M. De Pas,[12] Dennis L. Carter,[13] Andrew J. Warner,[1] George B. Rodrigues[1]

Clinical Lung Cancer, Vol. 15, No. 5, 346-55
Keywords: Metastectomy, NSCLC, Oligometastases, Radiotherapy, SABR/SBRT

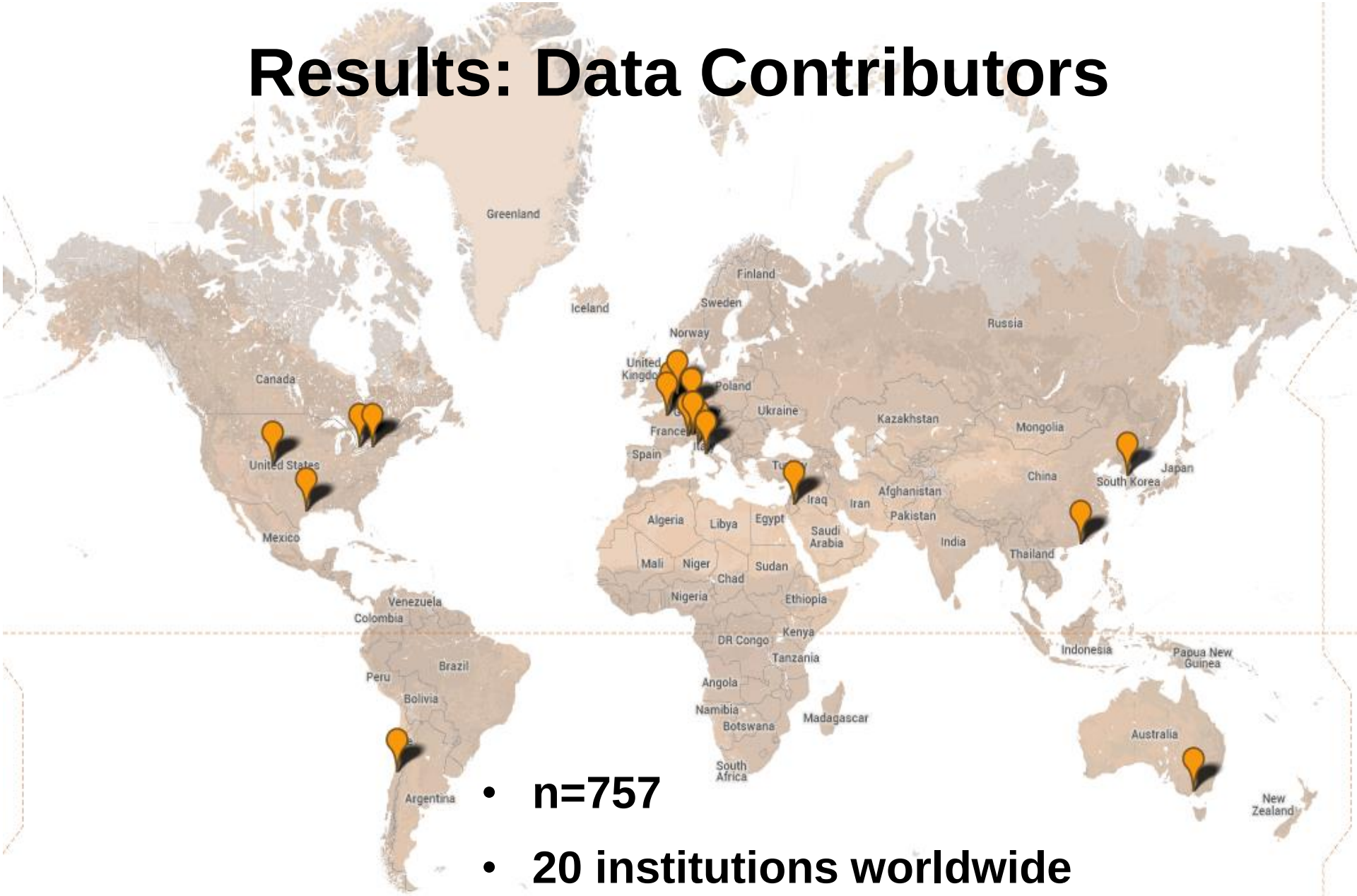
Objectives

- **To determine clinical outcomes associated with oligometastatic NSCLC.**
  - **overall survival (primary endpoint)**
  - **progression free survival**
- **To propose a potential risk stratification system for OS based on individual patient data to**
  - **drive clinical care**
  - **stratification of clinical trials**
  - **clinical trial eligibility**
  - **assist in the prediction of patient prognosis**

Methods

- **90 eligible studies**
- **Authors invited by email to submit individual patient datasets:**
  - **oligometastatic NSCLC 1-5 metastases (surgery/SRS/SABR)**
  - **controlled primary tumor (surgery/curative EBRT/SABR/SRS+/-chemo)**
  - **template data sheet supplied**

Results: Data Contributors



- n=757
- 20 institutions worldwide

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Methods

- **Patients divided randomly into training and validation sets (2/3 vs. 1/3 of patients)**
- **Univariable and Multivariable Cox regression: predictors of OS in training set**
- **Performance of multivariable model evaluated using validation set**
  - **P-value**
  - **Discrimination (c-statistic)**
- **Recursive Partitioning Analysis: risk groups**
- **Primary Endpoint: Overall Survival**
  - **date of Rx metastases to date of death**
- **Secondary Endpoint: Progression Free Survival**
  - **date of Rx metastases to date of first progression, local or distant**

Patient Characteristics

Variable	No. with data available	Median (range) or n (%)
Male Female	671	483 (72.0%) 188 (28.0%)
Median Age	712	61.1 yrs
Synchronous Metachronous	605	457 (75.5%) 148 (24.5%)
T Stage T1 T2 T3 T4	655	 163 (24.9%) 348 (53.1%) 110 (16.8%) 34 (5.2%)
Thoracic Stage I II III	652	 274 (42%) 154 (23.7%) 224 (34.3%)

Variable	No. with data available	Median (range) or n (%)
Good Performance Status	358	352 (98.3%)
No. of Oligometastases 1 2 3 4 5	757	 668 (88.2%) 63 (8.3%) 12 (1.6%) 9 (1.2%) 5 (0.7%)
Location of Oligometastases Adrenal Bone Brain Lung Liver Lymph Node Other	757	 98 (13.0%) 64 (8.5%) 269 (35.5%) 254 (33.6%) 18 (2.4%) 18 (2.4%) 59 (7.8%)
N Stage N0 N1 N2 N3	658	 342 (52.0%) 129 (19.6%) 171 (26.0%) 16 (2.4%)
Histology Adenocarcinoma Large Cell Squamous Other	743	 499 (67.2%) 57 (7.7%) 166 (22.3%) 21 (2.8%)

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Primary and Metastases Treatment

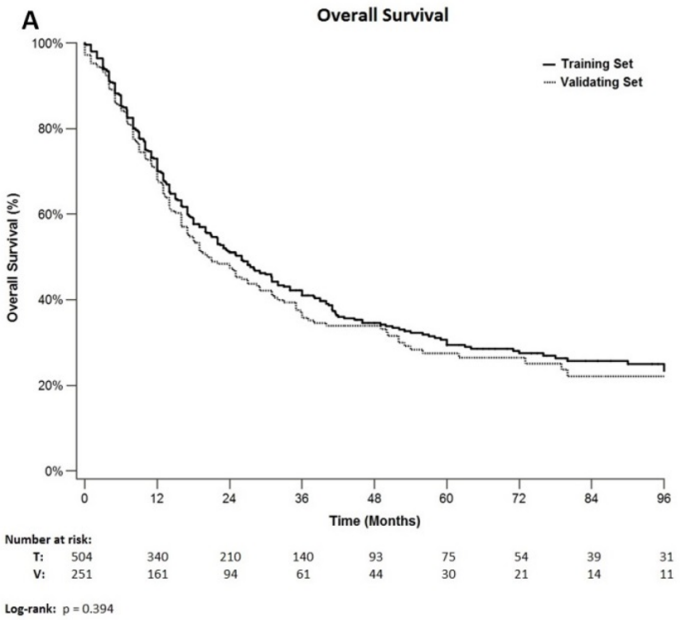
Primary

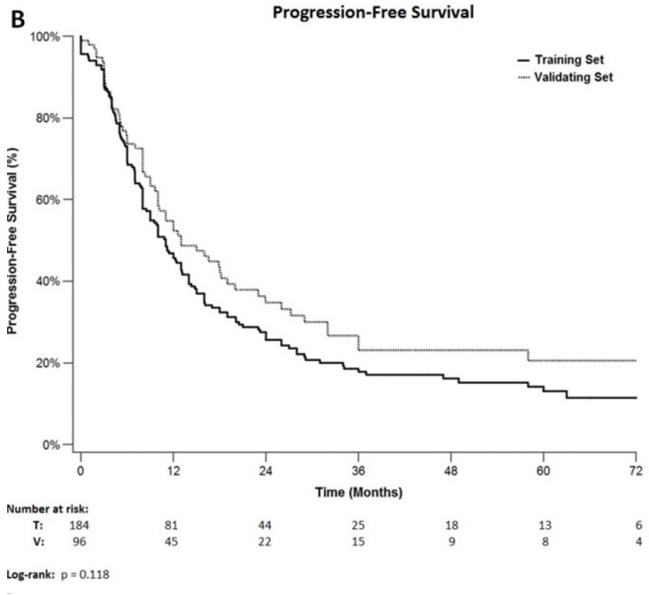
Radiotherapy:	n=122 (16.1%)
EBRT	94 (12.4%)
SBRT/SABR	28 (3.7%)
Surgery:	**n=635 (83.9%)**
Surgery	609 (80.4%)
Surgery + EBRT	26 (3.4%)

Metastases

Radiotherapy:	n=205 (37.7%)
EBRT	28 (5.2%)
SBRT/SABR	88 (16.2%)
SRS	62 (11.4%)
RT (Other)	27 (5.0%)
Metastectomy:	**n=339 (62.3%)**
Surgery	285 (52.4%)
Surgery + EBRT	3 (0.6%)
Surgery + SABR	3 (0.6%)
Surgery + SRS	1 (0.2%)
Surgery + RT	47 (8.6%)

Results: OS/PFS





Median OS: 26 months

1 yr OS: 70.2%
2 yr OS: 51.1%
5 yr OS: 29.4%
8 yr OS: 23.4%

Median PFS: 11 months

1 yr PFS: 45.7%
2 yr PFS: 25.6%
5 yr PFS: 13.1%

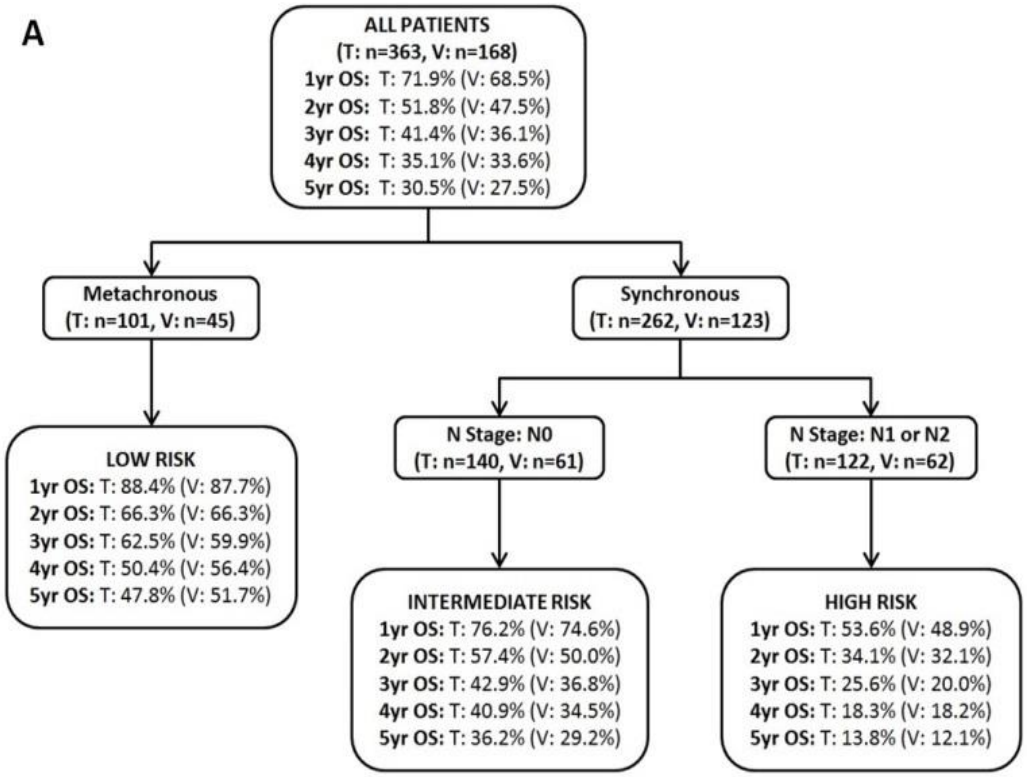
Predictors of OS: Validation Set

	Overall Survival	
Factor	**Multivariable Hazard Ratio (95% CI)**	**p-value**
Timing of Metastatic Disease (Synchronous vs. Metachronous)	3.02	< 0.001
N Stage		**0.002
N0	1 Reference	
N1	1.69 (1.00, 2.85)	0.051
N2	1.93 (1.25, 2.97)	0.003
N3	8.28 (1.82, 37.68)	0.006
Histology		**0.001
Adenocarcinoma	1 Reference	
Large Cell	2.39 (1.26, 4.51)	0.007
Squamous	1.86 (1.16, 2.98)	0.01
Other	6.26 (1.38, 28.38)	0.017

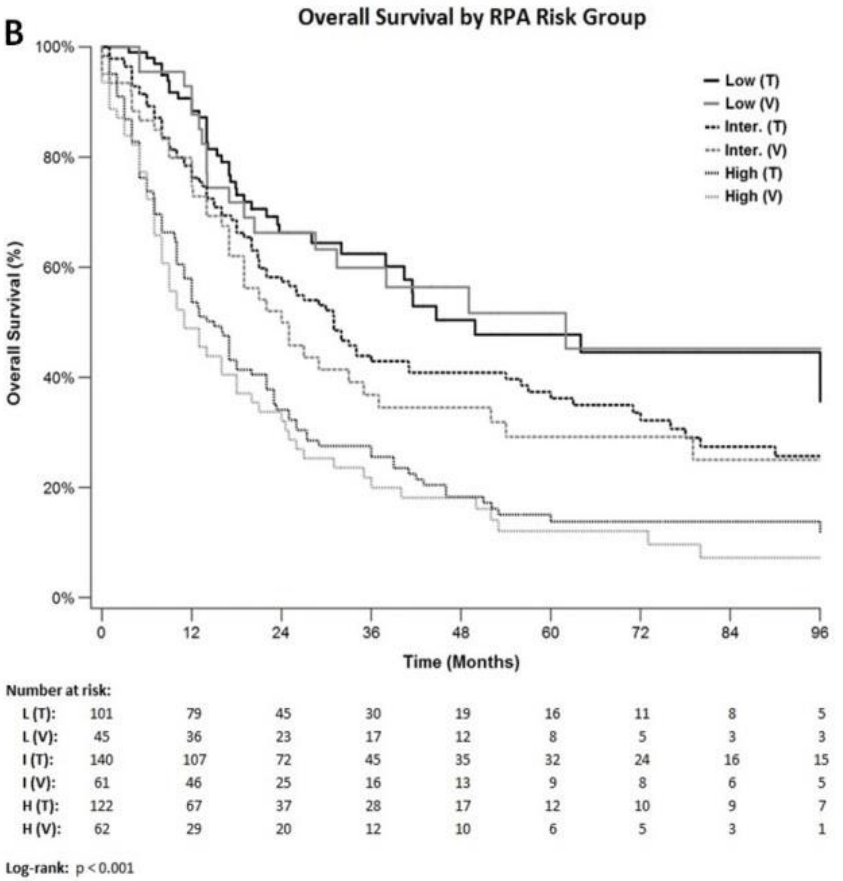
C-statistic: 0.682

Risk Classification Scheme: OS

A



B



Conclusions

- **Significant OS differences with patients stratified type of metastatic presentation (synchronous/metachronous) and N-stage**
- **Longer-term survival in patients with metachronous metastases**
- **Importance of nodal disease extent previously observed**
  - **Parikh et al., Int J Radiat Oncol Biol Phys 2014 Jul 15;89(4):880-7.**
- **Limitations: retrospective data, primarily single mets, lack of external validation**
- **The OS risk classification scheme may be considered for clinical decision making and to guide selection of patients for clinical trials of ablative treatment**

Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD, Andrea Riccardo Filippi, MD,† Juliette Thariat, MD,‡ Francoise Mornex, MD, PhD,‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD†*

TABLE 2. Ongoing Clinical Trials Examining the Role for Surgery or SABR for Oligometastatic Cancer

Study	Design	Eligibility	Intervention	Primary Endpoint
PulMICC[38]	Randomized phase II	Pulmonary metastases from colorectal cancer	Active monitoring vs. pulmonary metastasectomy	Feasibility/survival
SABR-COMET[39]	Randomized phase II	All treatable metastatic sites; maximum of three tumors to any single organ system; controlled primary tumor	Palliative-scheme radiation as clinically indicated vs. stereotactic ablative radiation to multiple sites	Overall survival
SAFRON II[40]	Randomized phase II	A maximum of three metastases to the lung from any nonhematological malignancy	Stereotactic multifraction SABR vs. radiosurgery	Toxicity
NCT01185639[41]	Phase II	NSCLC with ≤5 metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have three mets	SBRT to affected sites, delivered in three or five fractions	Progression-free survival
NCT01725165[72]	Randomized phase II	Three or less metastases from NSCLC	Consolidative radiotherapy and/or surgery vs. systemic therapy or observation	Progression-free survival

Whether the oligometastatic state truly exists in NSCLC is unclear, because no NSCLC-specific randomized trials in this specific patient population have been completed

(*J Thorac Oncol.* 2014;XX: 00–00)