

▼
**Radiochirurgia e
Radioterapia stereotassica:**
▲
non solo tecnica



Associazione
Italiana
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Oncologica



Selezione dei pazienti

Andrea Filippi

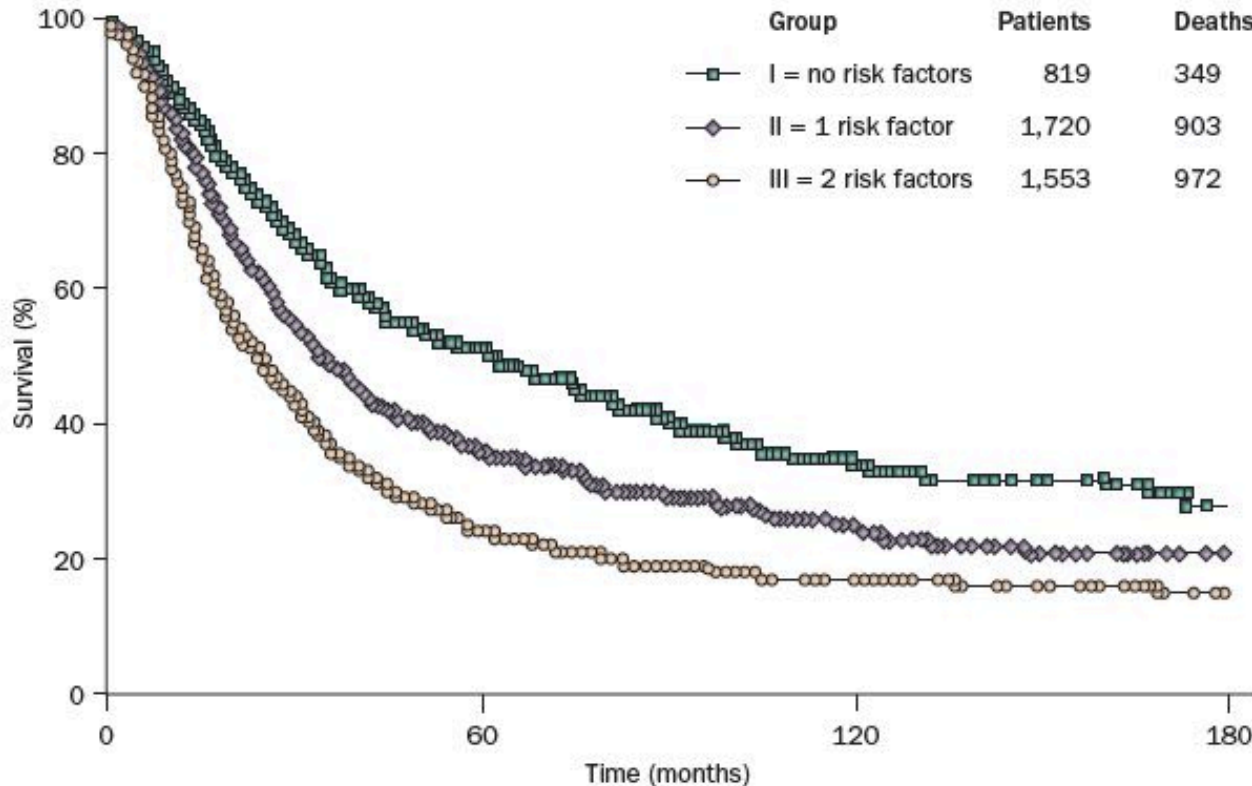
Dipartimento di Oncologia-Radioterapia S. Luigi
Gonzaga
Orbassano (TO)

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

International Registry of Lung Metastases

Ugo Pastorino, MD

UNIVERSITY OF TORINO DEPARTMENT OF ONCOLOGY



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

Liver metastases: selected surgical series

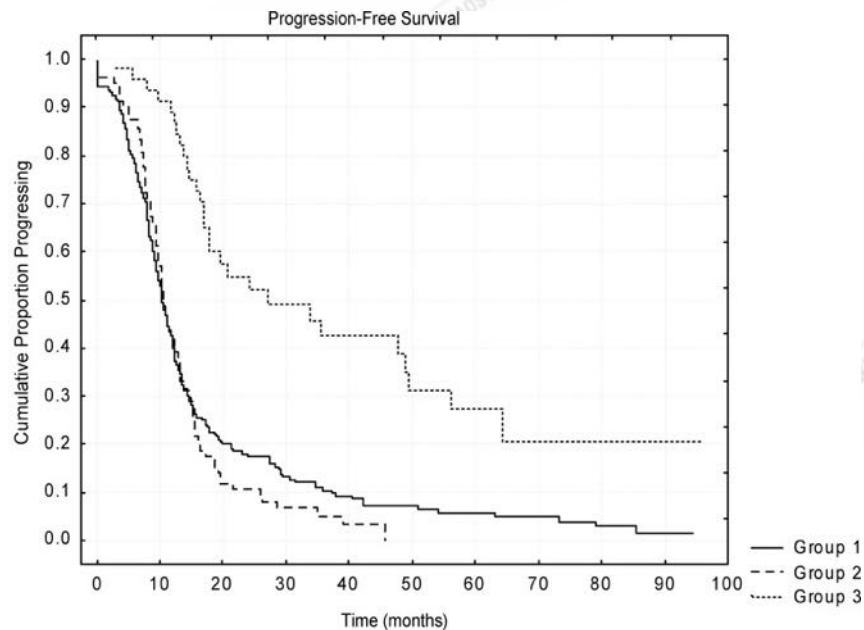
Study	n	5-yr OS	10-yr OS	Prognostic factors
Hughes et al. (1986)	607	33%	No 10-yr fu	Positive margins Bilobar disease
Nordinger et al. (1996)	1568	28%	No 10-yr fu	Positive margins Large size High number CEA levels
Fong et al. (1999)	1001	37%	22%	Extrahepatic disease Short interval between primary and met
Pawlik et al. (2005)	557	58%	No 10-yr fu	Positive margins > 3 mets CEA level > 200 ng/ml





The Role of Lung Metastasis Resection in Improving Outcome of Colorectal Cancer

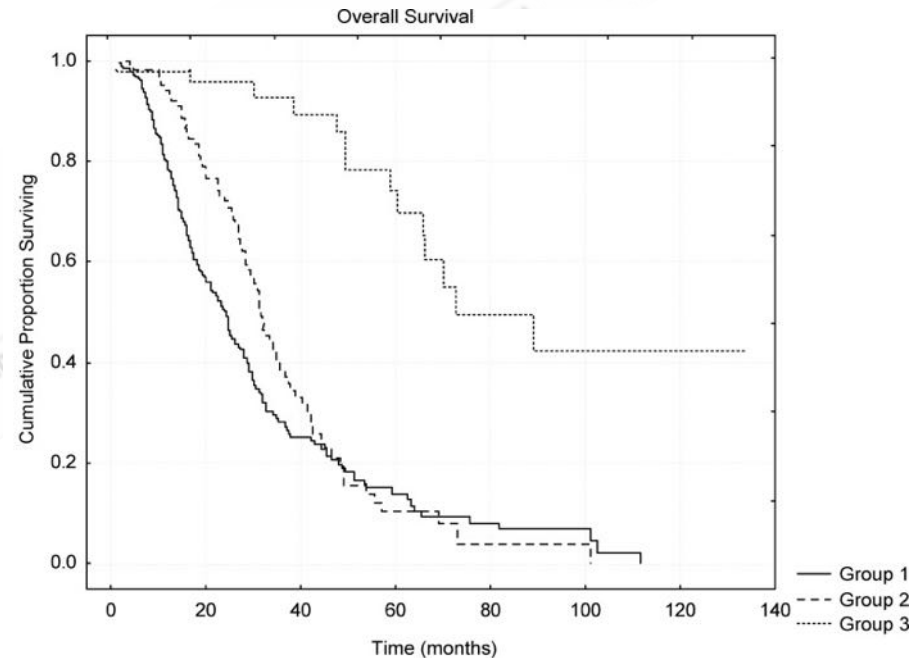
Progression-free survival



Patients at risk

Group 1	255	122	40	24	16	9	6	5	3	1
Group 2	104	55	11	5	2	0	0	0	0	0
Group 3	50	40	22	18	13	8	5	3	2	1

Overall survival



Patients at risk

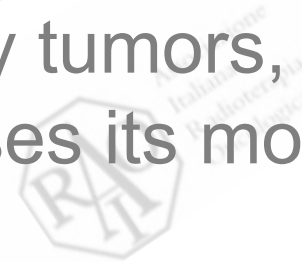
Group 1	255	112	36	12	7	3	1
Group 2	104	71	23	4	1	1	0
Group 3	50	37	18	17	7	3	3

<p>Group 1 Lung and extrapulmonary metastases 255 patients</p>	<p>Group 2 Only lung metastases not submitted to surgery 104 patients</p>	<p>Group 3 Only lung metastases submitted to surgery 50 patients (19 after CT)</p>
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Radiotherapy in Oligometastases

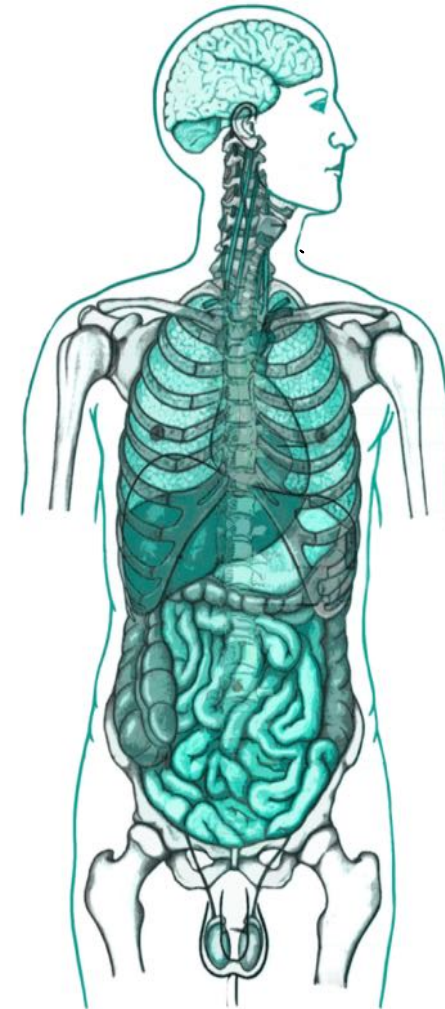
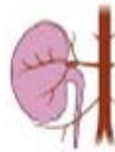
“Conformal radiation therapy, now being investigated for the treatment of primary tumors, may find the treatment of oligometastases its most important application”

Hellmann and Weichselbaum, JCO 1995



SABR: treatable metastatic sites

- Lung
- Liver
- Adrenal gland
- Spinal metastases
- Bone
- Lymphnodes



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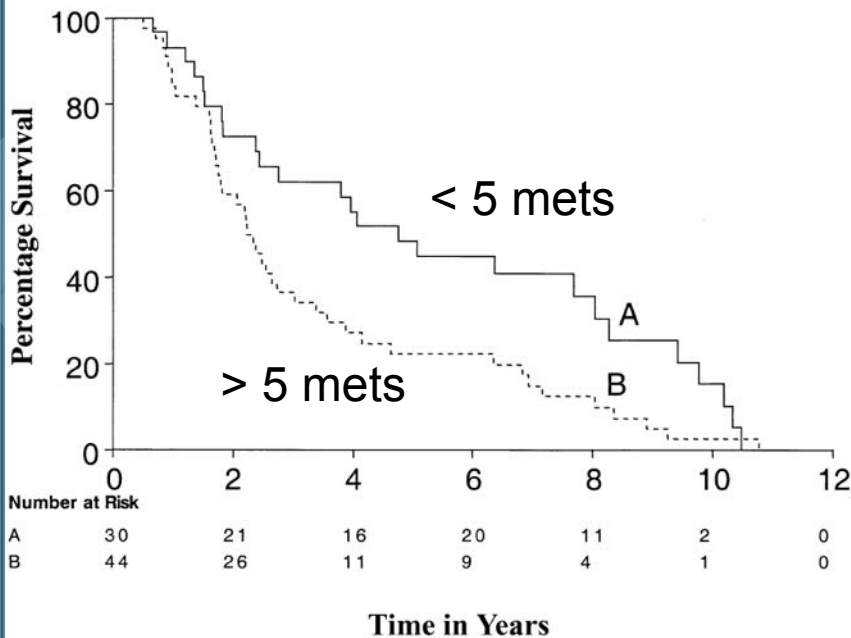
CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VAL

CONVEGNO DEL GRUPPO REGIONALE PIEMONTE

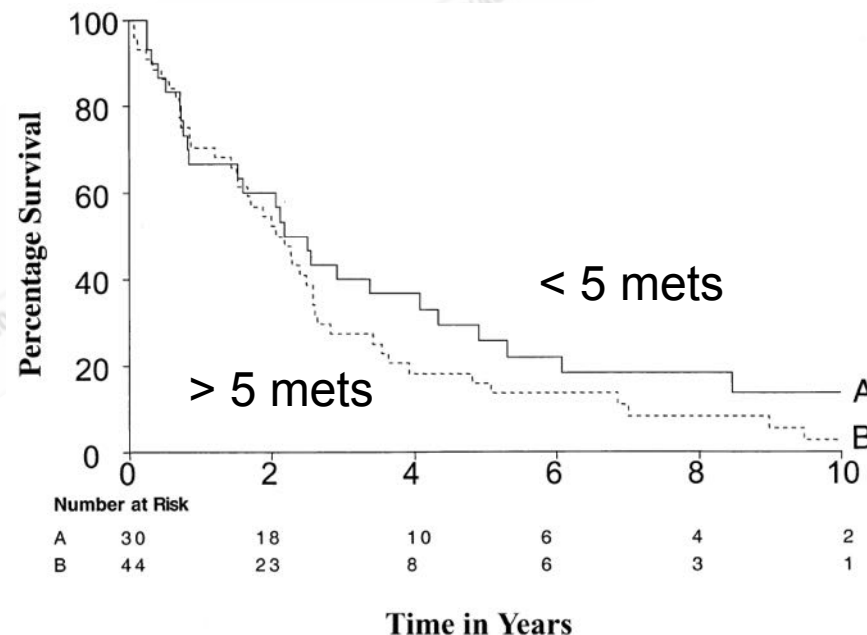
CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIG



Oligometastases: definition?



PFS



OS

Singh et al, IJROBP 2004



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

Oncologist. 2012;17(8):1100-7.

Table 1. Outcomes of stereotactic body radiation therapy for lung metastases from selected trials

Study	<i>n</i> of patients	Median dose/ <i>n</i> of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 48% 2-yr, 21%	Grade 3, 1 (3.7%) Grade 5, 1 (3.7%)
Yoon et al. [71]	53	30 Gy/3; 40 Gy/4; 48 Gy/4	14 (4–56)	70% for 30 Gy, 77% for 40 Gy, 100% for 48 Gy	1-yr, 89%; 2-yr, 51%	Grade ≥2, 0%
Okunieff et al. [18]	50	50 Gy/10; 48 Gy/6; 57 Gy/3	18.7 (3.7–60.9)	3-yr, 91%	2-yr, 50%	Grade 2, 6.1% Grade 3, 2%
Norihisa et al. [6]	34	48 Gy/4; 60 Gy/5	27 (10–80)	2-yr, 90%	2-yr, 84%	Grade 2, 4 (12%) Grade 3, 1 (3%)
Brown et al. [72]	35	5 Gy/1 to 60 Gy/4	18 (2–41)	Crude, 77%	2-yr, 72.5%	Grade 3–4, 1 (2.8%)
Rusthoven et al. [14]	38	60 Gy/3	15.4 (6–48)	2-yr, 96%	2-yr, 39%	No grade 4 Grade 3, 3 (8%)
Ricardi et al. [17]	61	45 Gy/3; 26 Gy/1	20.4 (3–77)	2-yr, 89%	2-yr, 66.5	Grade 3, 1 (1.6%)

Stereotactic Body Radiotherapy for Multisite Extracranial Oligometastases

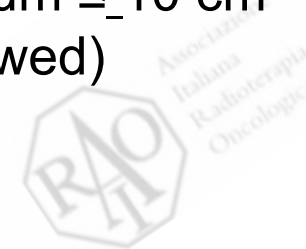
Final Report of a Dose Escalation Trial in Patients With 1 to 5 Sites of Metastatic Disease

Joseph K. Salama, MD¹; Michael D. Hasselle, MD²; Steven J. Chmura, MD, PhD^{2,3}; Renuka Malik, MD²; Neil Mehta, MD²; Kamil M. Yenice, MD²; Victoria M. Villaflor, MD^{3,4}; Walter M. Stadler, MD^{3,4}; Philip C. Hoffman, MD^{3,4}; Ezra E. W. Cohen, MD^{3,4}; Philip P. Connell, MD^{2,3}; Daniel J. Haraf, MD^{2,3}; Everett E. Vokes, MD^{2,3,4}; Samuel Hellman, MD²; and Ralph R. Weichselbaum, MD^{2,3,5}

ELIGIBILITY CRITERIA: 1-5 mts, PS ECOG \leq 2, mts dm \leq 10 cm or mts volume \leq 500 mL, no CT during SBRT (HT allowed)

- 61 eligible pts (113 metastatic sites)
- 80% received prior CT for metastatic disease (37% had previous mts-directed therapies)

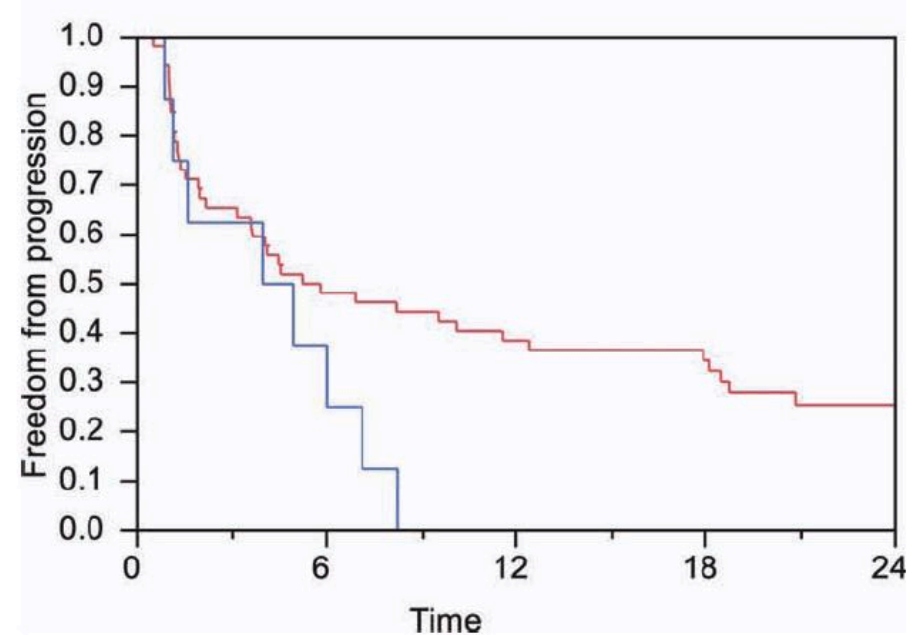
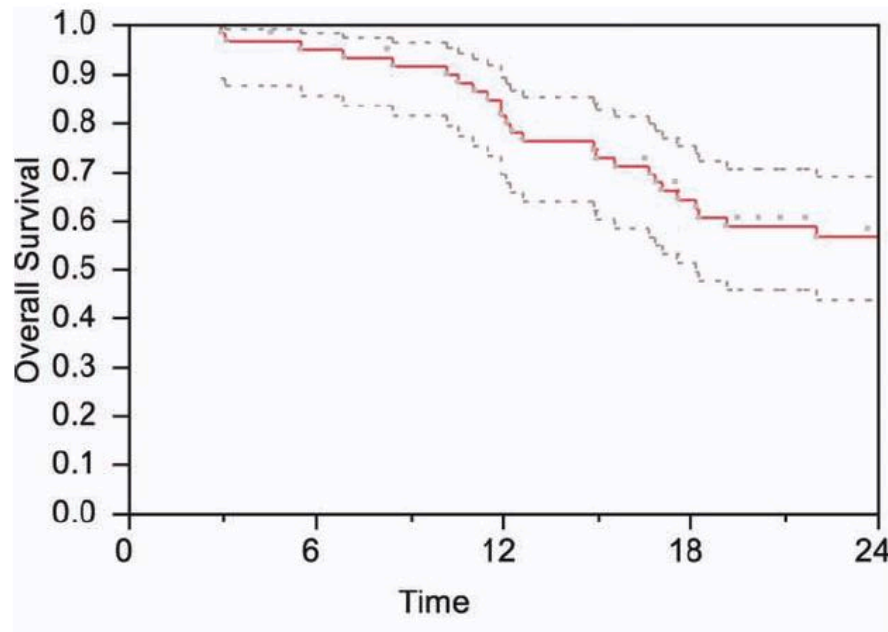
Cancer, 2012



2-year survival rate: 56.7%

Non-surgical metastasis-directed therapy could render patients free of active measurable disease

Procedure well tolerated without undue toxicity (12% \geq G3)

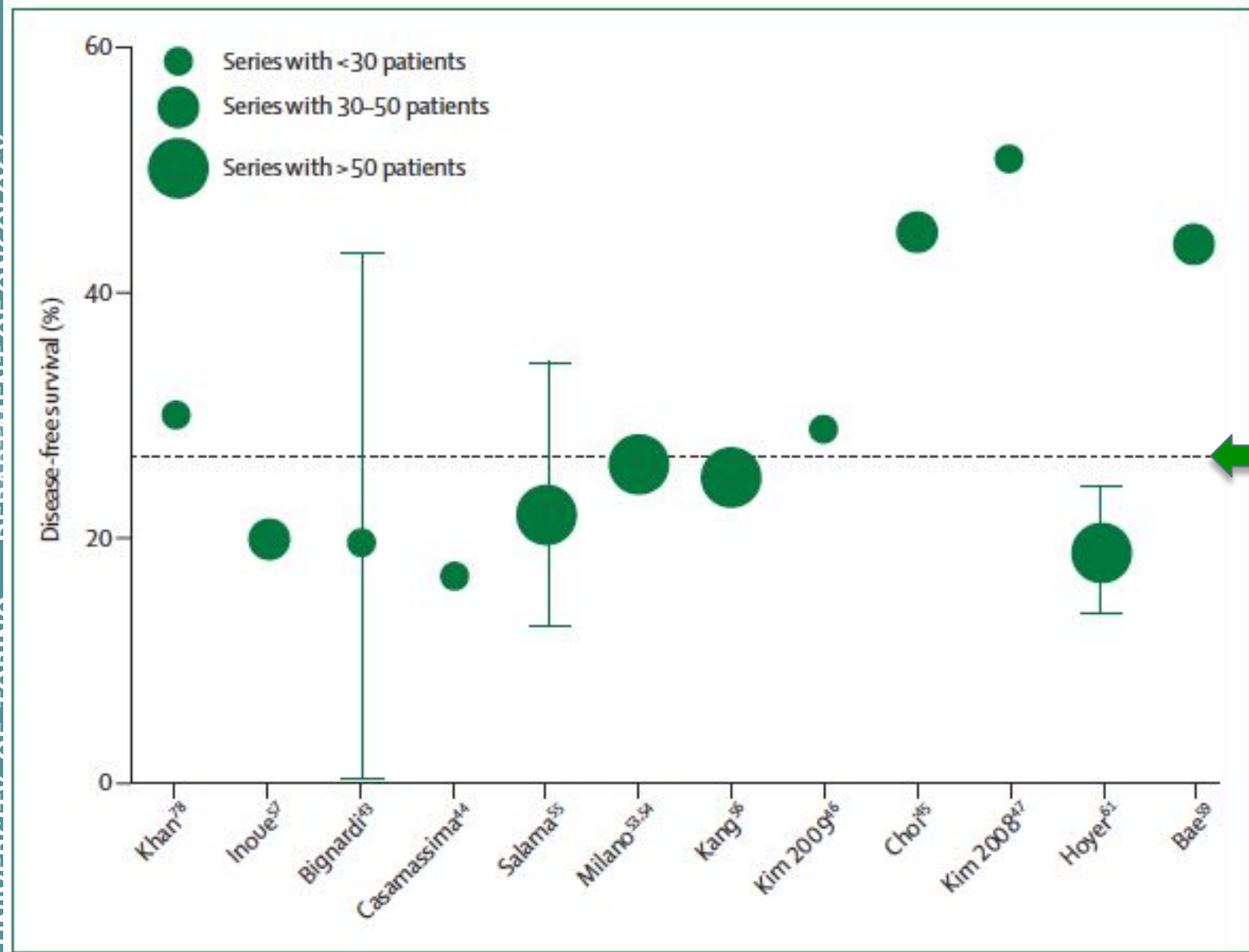


NUMBER OF METS (1-3 vs 4-5) CAN SELECT PTS WITH FAVOURABLE OLIGOMETASTATIC DISEASE



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Mean DFS

Tree et al, Lancet Oncology 2013

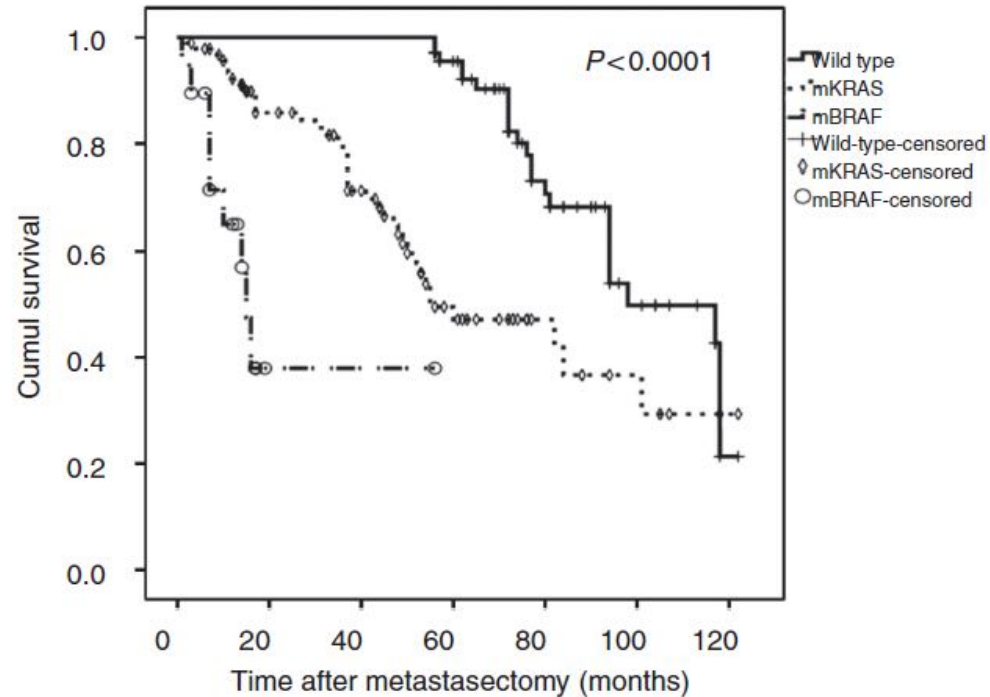


Is it the selection rather than the surgery that explains the survival difference?



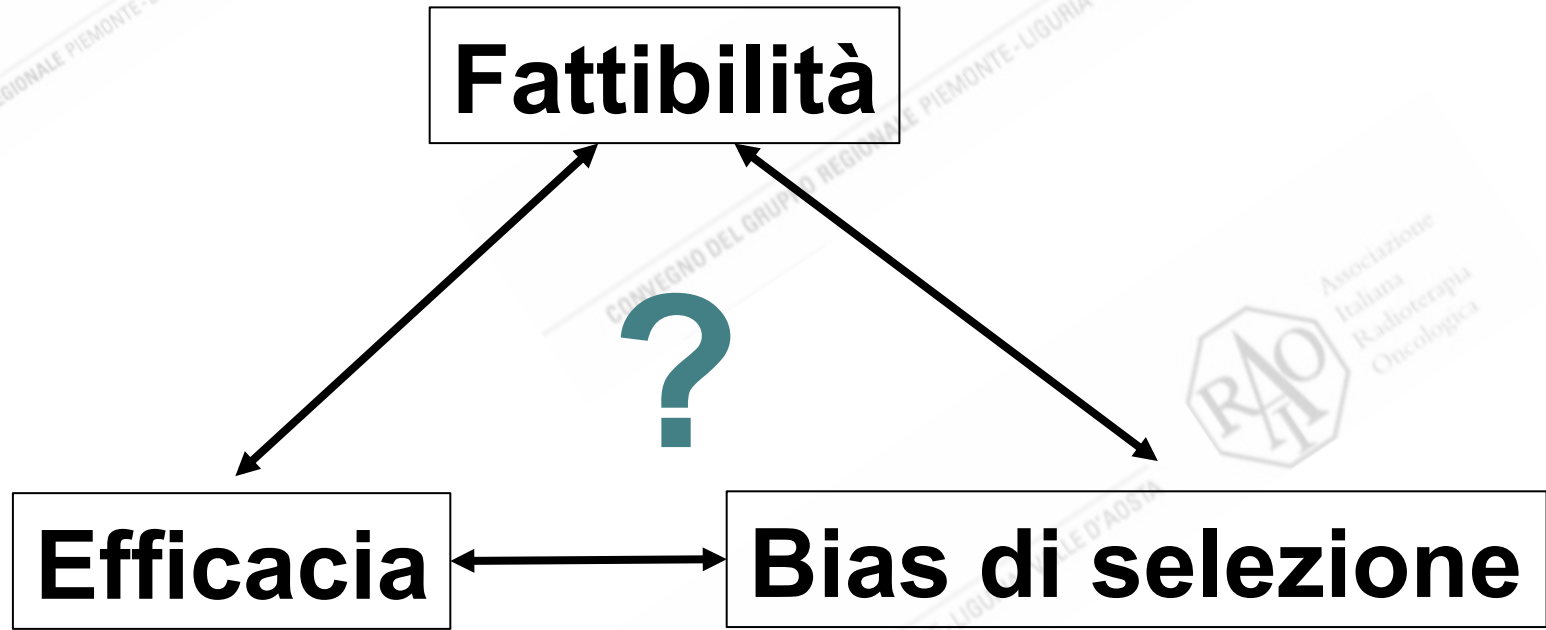
Utley & Treasure. J Thorac Oncol 2010; Vol 5 (suppl 6): S200-S202

Colorectal cancer: prognostic impact of KRAS and BRAF after lung metastasectomy



Patients at risk wild type	68	68	68	58	29	12	1
Patients at risk mKRAS	93	63	46	20	9	5	1
Patients at risk mBRAF	19	1	1	0	0	0	0

Figure 1. The Kaplan–Meier OS according to the mutational status (WT, mKRAS, mBRAF).



CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VALLE D'AOSTA

CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VALLE D'AOSTA

CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VALLE D'AOSTA

LUNG OLIGOMETASTASES: WHO IS THE PERFECT CANDIDATE FOR SBRT ?



Based on published studies, patients who might benefit the most from SBRT are:

- ✓ breast histology,
- ✓ disease-free interval ≥ 12 months,
- ✓ control of the primary tumor,
- ✓ small lesions,
- ✓ limited number of lesions (up to three)
- ✓ higher radiation dose delivered (BED > 100 Gy).

Salama, et al Cancer 2011

Wersall, et al Radiother Oncol 2005

Ricardi, et al Lung Cancer 2012

Louie, et al Int J Radiat Oncol Biol Phys (Suppl) 2014

SBRT VS METASTASECTOMY: WHAT'S THE BEST COST/EFFECETIVENESS CHOICE?



NO RANDOMIZED TRIALS, THUS NO EVIDENCES?

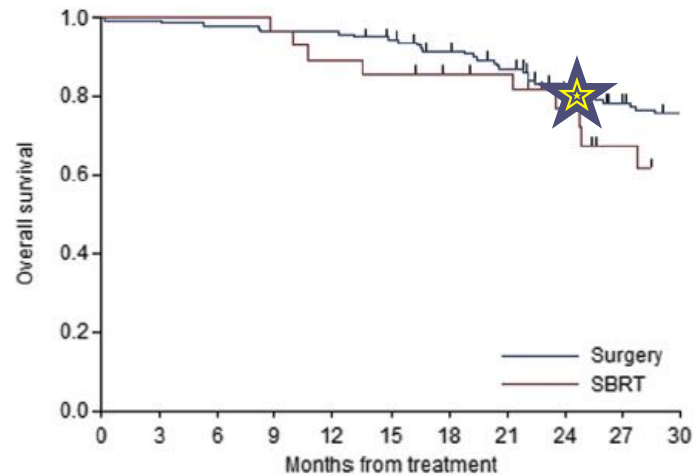
SBRT VS METASTASECTOMY: WHAT'S THE BEST COST/EFFECTIVE CHOICE?



Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer

A.R. Filippi^{*}, F. Guerrera[†], S. Badellino^{*}, M. Ceccarelli[‡], A. Castiglione[‡], A. Guarneri^{*}, R. Spadi[§], P. Racca[§], G. Ciccone[‡], U. Ricardi^{*}, E. Ruffini[†]

^{*} Department of Oncology, Radiation Oncology, University of Torino, Italy

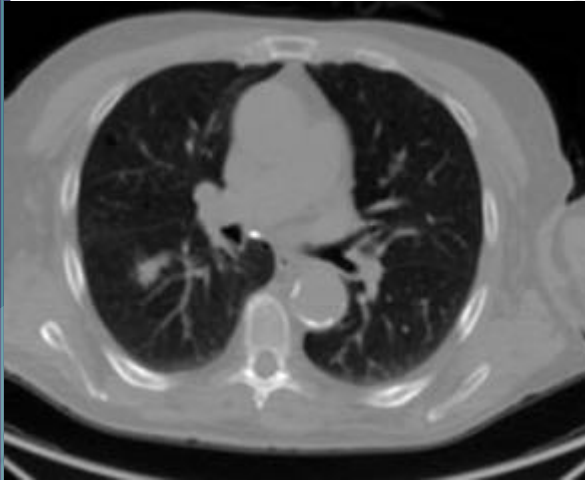


Number at risk							
Surgery	142	139	137	124	103	88	
SBRT	28	28	25	22	17	10	

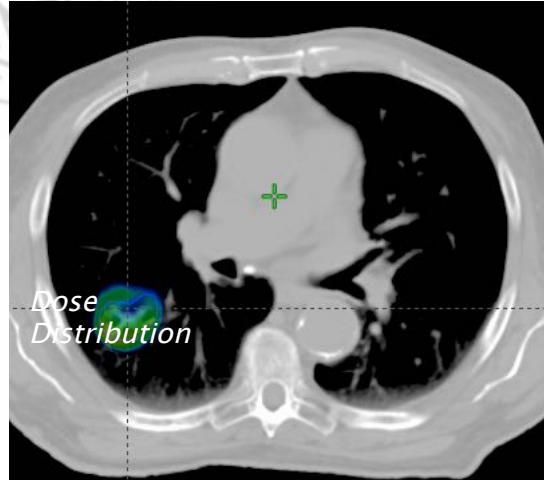
Fig 1. Overall survival according to the treatment received.

Conclusion: With limitations consisting in the retrospective observational design and different sample sizes, the results of this explorative analysis indicate that overall survival probability after SBRT is similar to surgery for the first 2 years from treatment. This finding supports the need for high-quality trials comparing different treatment modalities for lung oligometastases from CRC.

COLORECTAL LUNG OLIGOMTS PARADIGMATIC CASE



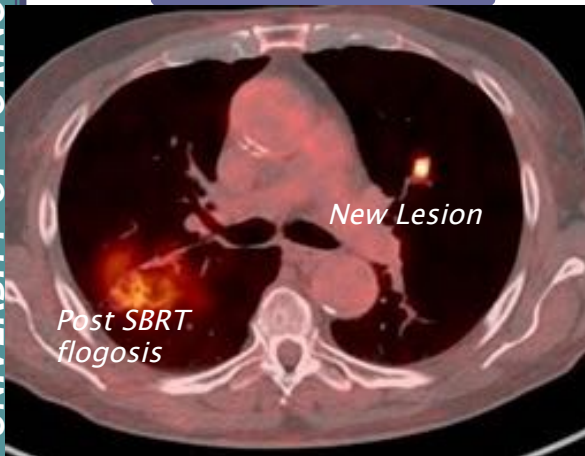
CT before SBRT



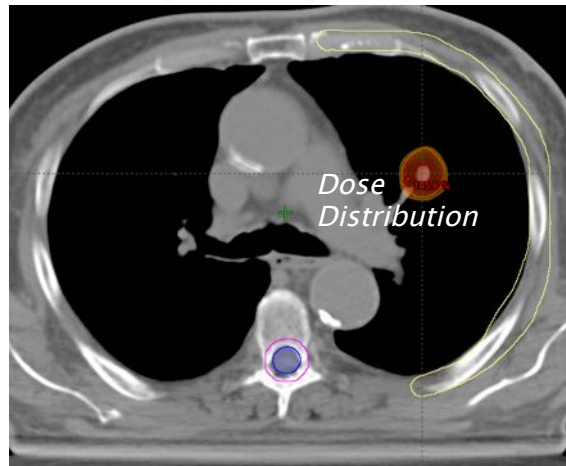
48 Gy/4 fr.



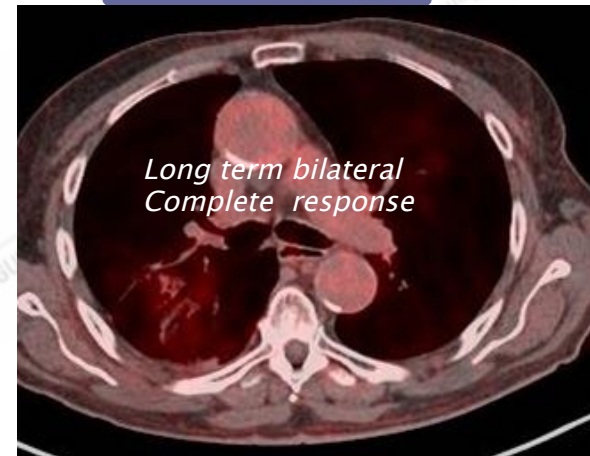
CR @ 3 months



9 months re-evaluation PET-CT



50 Gy/5 fr.

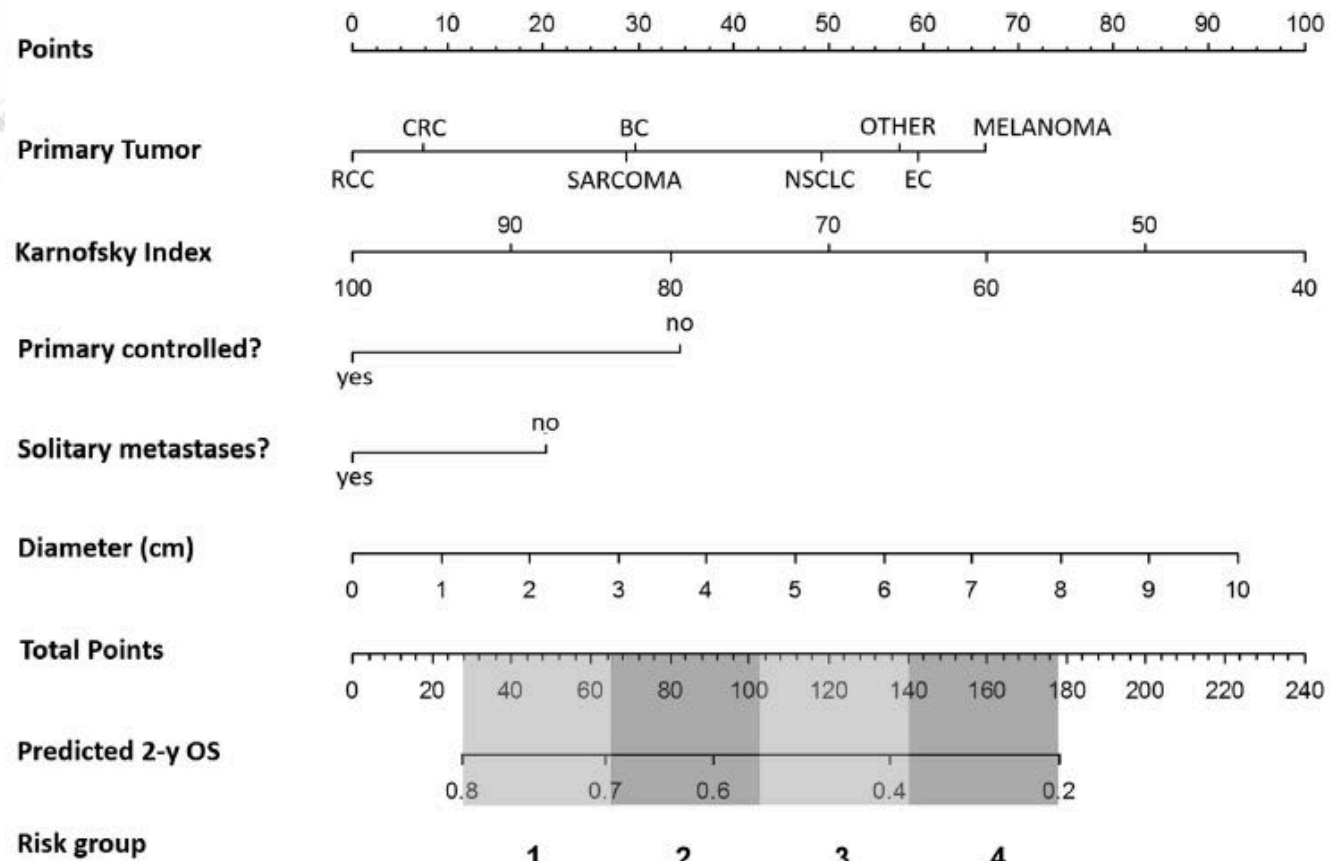


CR @ 24 months

Courtesy F. Alongi

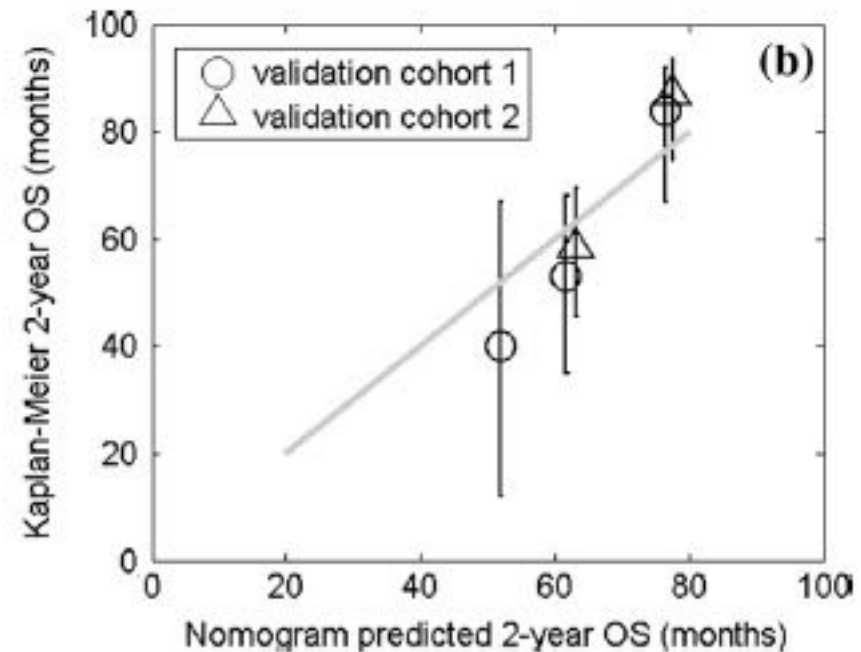
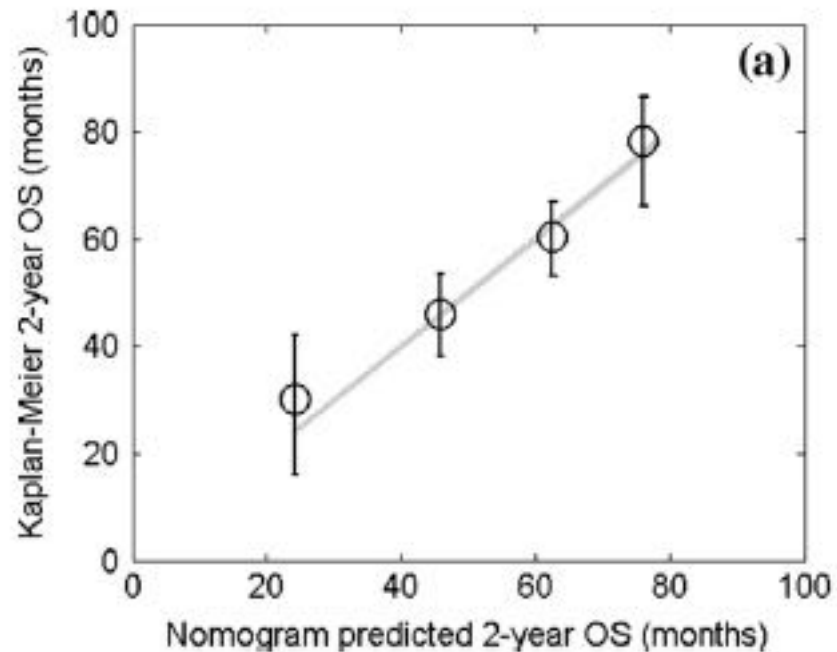
Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease ☆☆☆

S. Tanadini-Lang^{a,1}, J. Rieber^{b,c,1}, A.R. Filippi^d, M.M. Fode^e, J. Streblow^{b,c}, S. Adebahr^f, N. Andratschke^{a,g}, O. Blanck^h, J. Boda-Heggemannⁱ, M. Duma^j, M.J. Eble^k, I. Ernst^l, M. Flentje^m, S. Gerumⁿ, P. Hass^o, C. Henkenberens^p, G. Hildebrandt^g, D. Imhoff^q, H. Kahl^r, N.D. Klass^s, R. Krempien^t, F. Lohaus^{u,v,w}, C. Petersen^x, E. Schrade^y, T.G. Wendt^z, A. Wittig^{aa}, M. Høyer^{ab}, U. Ricardi^d, F. Sterzing^{b,c,ac}, M. Guckenberger^{a,*}



Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease ☆☆☆

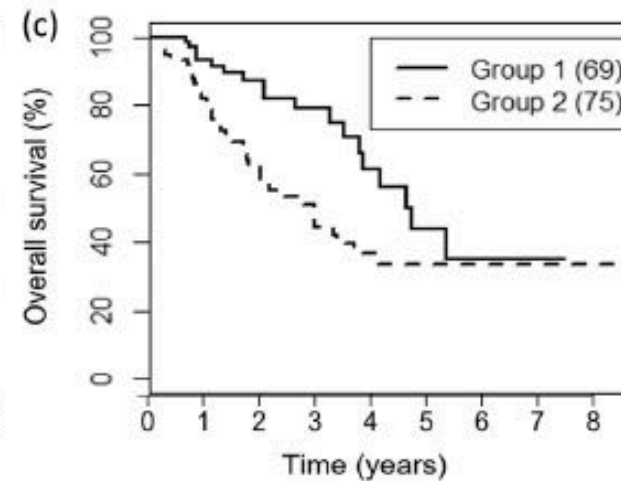
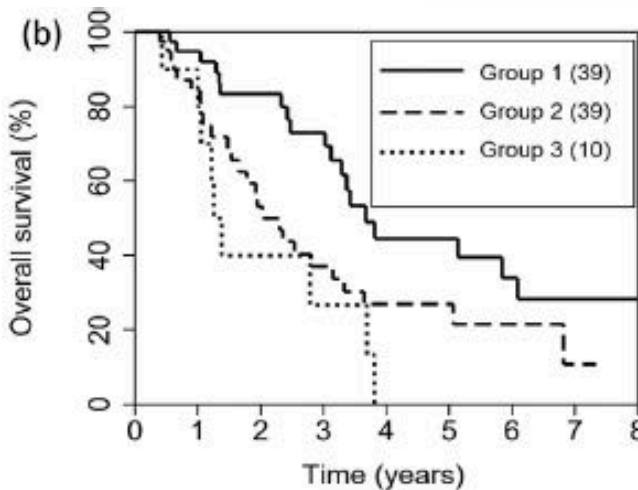
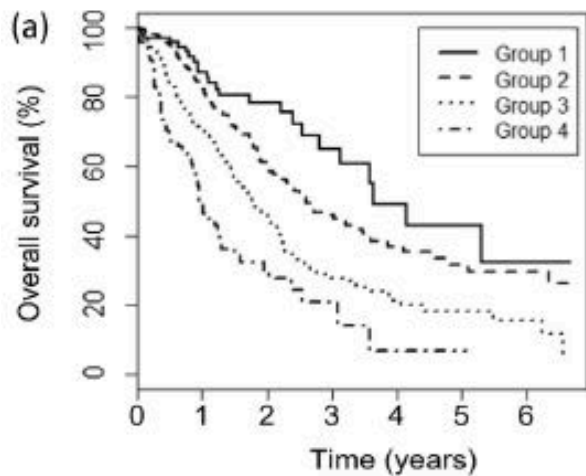
S. Tanadini-Lang^{a,1}, J. Rieber^{b,c,1}, A.R. Filippi^d, M.M. Fode^e, J. Streblow^{b,c}, S. Adebahr^f, N. Andratschke^{a,g}, O. Blanck^h, J. Boda-Heggemannⁱ, M. Duma^j, M.J. Eble^k, I. Ernst^l, M. Flentje^m, S. Gerumⁿ, P. Hass^o, C. Henkenberens^p, G. Hildebrandt^g, D. Imhoff^q, H. Kahl^r, N.D. Klass^s, R. Krempien^t, F. Lohaus^{u,v,w}, C. Petersen^x, E. Schrader^y, T.G. Wendt^z, A. Wittig^{aa}, M. Høyer^{ab}, U. Ricardi^d, F. Sterzing^{b,c,ac}, M. Guckenberger^{a,*}





Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease ☆☆☆

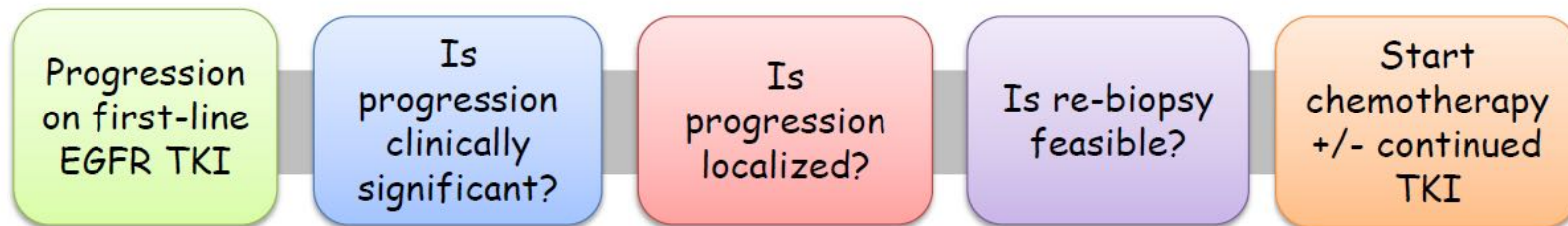
S. Tanadini-Lang^{a,1}, J. Rieber^{b,c,1}, A.R. Filippi^d, M.M. Fode^e, J. Streblow^{b,c}, S. Adebahr^f, N. Andratschke^{a,g}, O. Blanck^h, J. Boda-Heggemannⁱ, M. Duma^j, M.J. Eble^k, I. Ernst^l, M. Flentje^m, S. Gerumⁿ, P. Hass^o, C. Henkenberens^p, G. Hildebrandt^g, D. Imhoff^q, H. Kahl^r, N.D. Klass^s, R. Krempien^t, F. Lohaus^{u,v,w}, C. Petersen^x, E. Schrader^y, T.G. Wendt^z, A. Wittig^{aa}, M. Høyer^{ab}, U. Ricardi^d, F. Sterzing^{b,c,ac}, M. Guckenberger^{a,*}



Patients at risk							
Group 1	101	60	38	17	9	8	4
Group 2	258	168	92	48	26	18	16
Group 3	237	124	61	34	16	11	2
Group 4	74	32	15	7	2	2	



Approach to the management of *EGFR* mutant NSCLC with progression on first-line *EGFR* TKI



There is not one uniform approach to treating resistance

Potential strategies at the time of clinical progression for oncogene addicted NSCLC

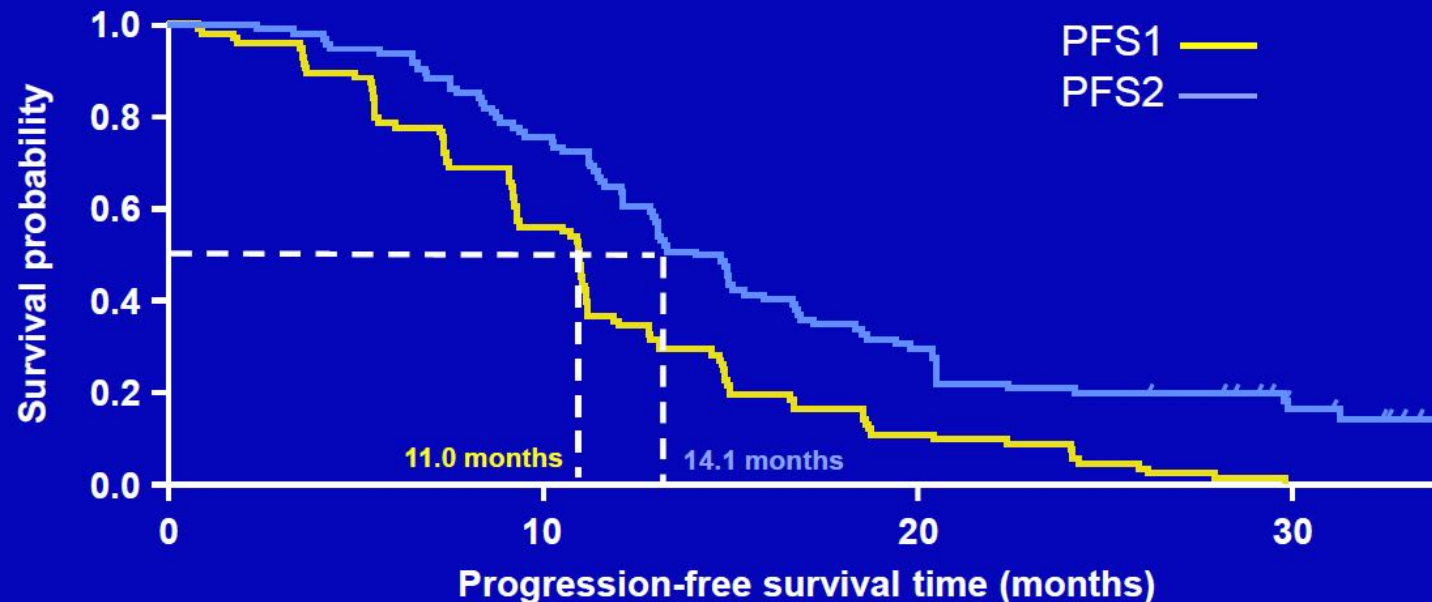
- Switch to chemotherapy
- Add chemotherapy
- Continue EGFR or ALK TKIs beyond progression
 - *Local therapies*
- Different targeted therapy based on specific resistance mechanism





Continuation of erlotinib post-PD extended PFS

- In patients receiving post-PD erlotinib (n=93)
 - PFS1 was 11.0 months
 - the difference between PFS1 and PFS2 was an additional **3.1 months**

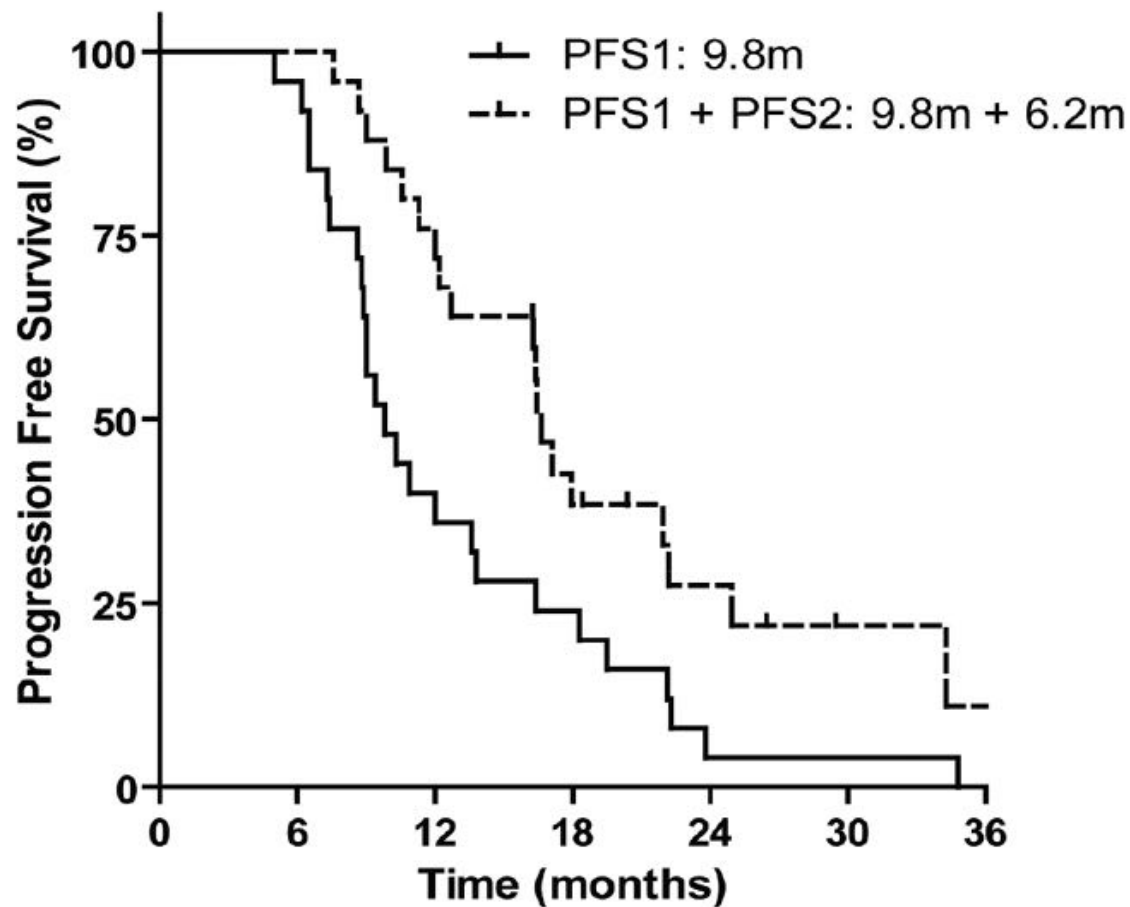


Local ablative therapy of oligoprogressive disease in oncogene-addicted NSCLC treated with TKI

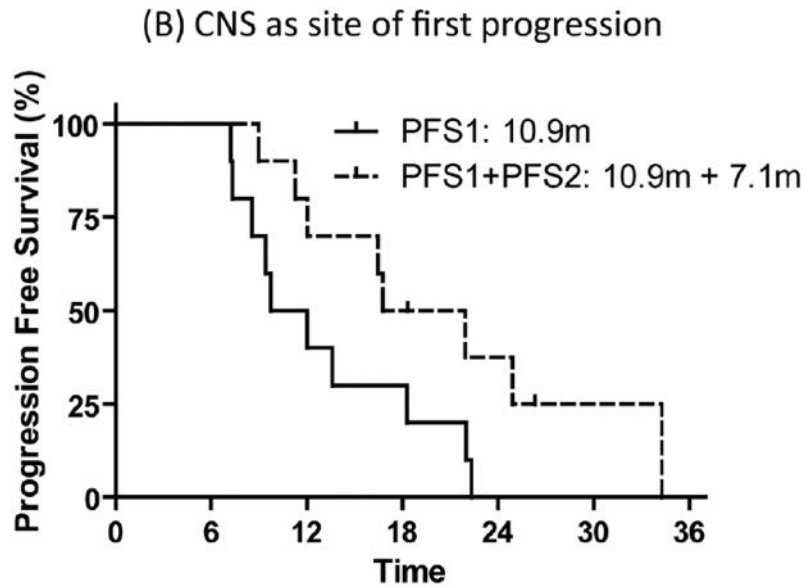
- Patients with metastatic ALK+ NSCLC treated with crizotinib (n=38) and EGFR-mut NSCLC treated with erlotinib (n=27)
- A subset of patients with either non-leptomeningeal CNS and/or ≤ 4 sites of extra-CNS progression (**oligoprogressive disease**) suitable for **local ablative therapy** received either **radiation** or **surgery** to these sites and continued on the same TKI.



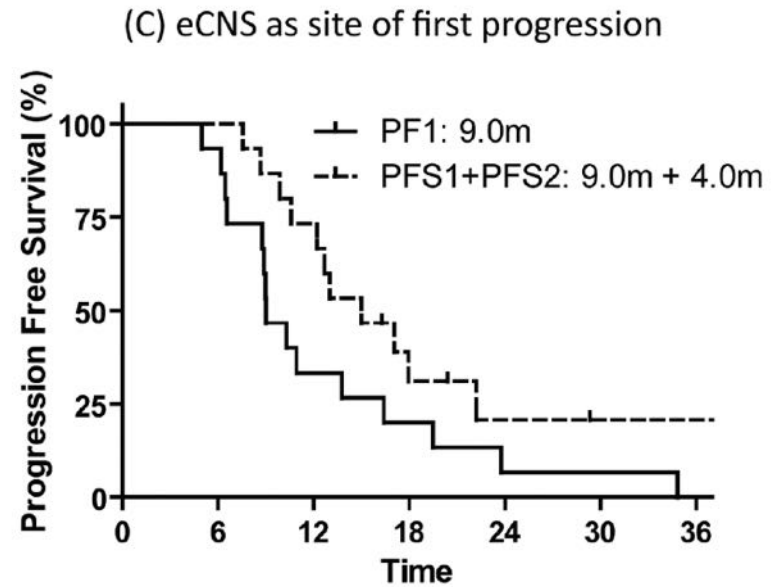
(A) PFS of all patients treated with LAT and continuation of TKI therapy



N = 25 patients



N = 10 patients



N = 15 patients
Including 3 patients with simultaneous
CNS + eCNS progression

Stereotactic Radiotherapy for Extra-CNS Oligoprogressive Disease in ALK+ Lung Cancer Patients on Crizotinib

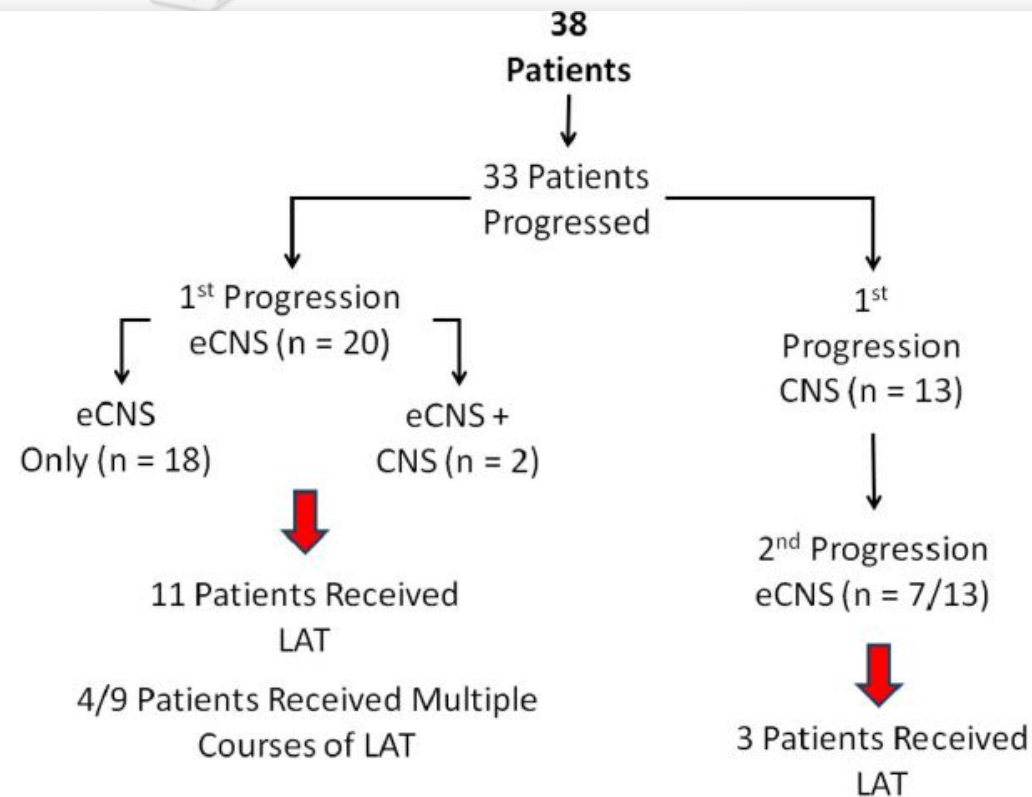


Figure 1.

Schema illustrating eCNS or CNS progression while on crizotinib and those with eCNS OPD considered appropriate for LAT.

Stereotactic Radiotherapy for Extra-CNS Oligoprogressive Disease in ALK+ Lung Cancer Patients on Crizotinib

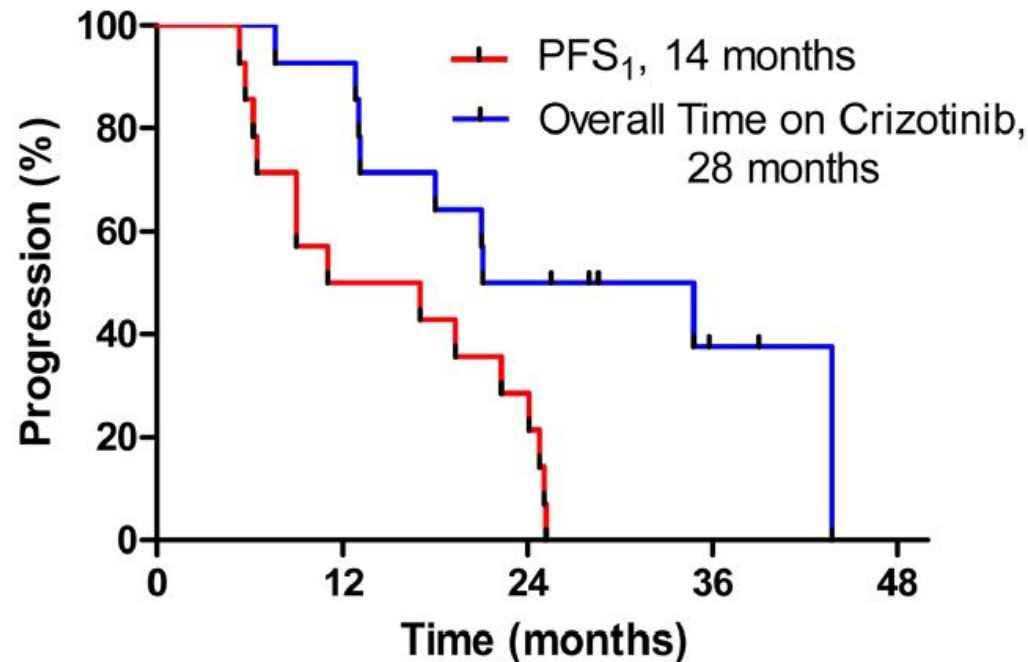


Figure 3.

Evaluating KM median PFS1 and overall time on crizotinib in patients who received eCNS LAT. Time is measured from start of crizotinib to time of first progression or maximum time while on crizotinib.

Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

Puneeth Iyengar, Brian D. Kavanagh, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, Paul A. Bunn, Hak Choy, and Robert Timmerman



Table 1. Baseline Characteristics of Patients Treated on Protocol

Characteristic	No.	%
Sex		
Female	11	46
Male	13	54
Age, years		
Median	66.9	
Standard deviation	7.6	
Range	56-86	
Previously treated brain metastases		
No	22	92
Yes	2	8
Follow-up, months		
Mean	16.8	
Standard deviation	14.5	
Range	3.4-60.3	
Study site		
University of Colorado	6	25
UT Southwestern Medical Center	18	75
Survival, last follow-up		
Alive	11	46
Dead	13	54
No. of previous systemic therapy regimens		
1	15	63
2	7	29
3	2	8
Race		
White, Hispanic	23	96
African American	1	4

Table 2. SBRT Treatment Patterns

Treatment Pattern	No.	%
SBRT sites treated per patient		
1	8	33
2	8	33
3	5	21
4	2	9
5	1	4
SBRT courses to specific sites		
18	Lungs (35% of 52 sites treated)	
13	Mediastinum/hilum (25)	
7	Adrenals (13)	
6	Bone/spine/chest wall (13)	
4	Liver/paracaval (8)	
3	Nonmediastinal lymph nodes (5)	
1	Kidney (1)	
Lesions treated with specific SBRT fractionation schemas		
21	3 fx to 27-33 Gy (40)	
21	5 fx to 35-40 Gy (40)	
10	1 fx to 19-20 Gy (20)	

Abbreviations: fx, fractions; SBRT, stereotactic body radiation therapy.

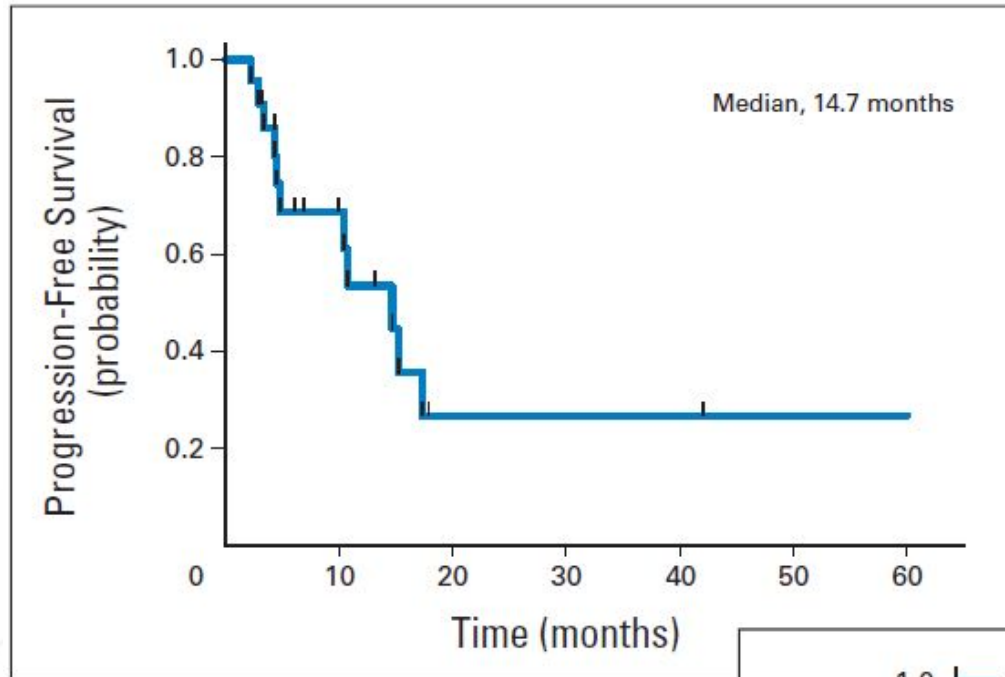


Fig 1. Kaplan-Meier analysis of progression-free survival for 24 patients enrolled on the study.

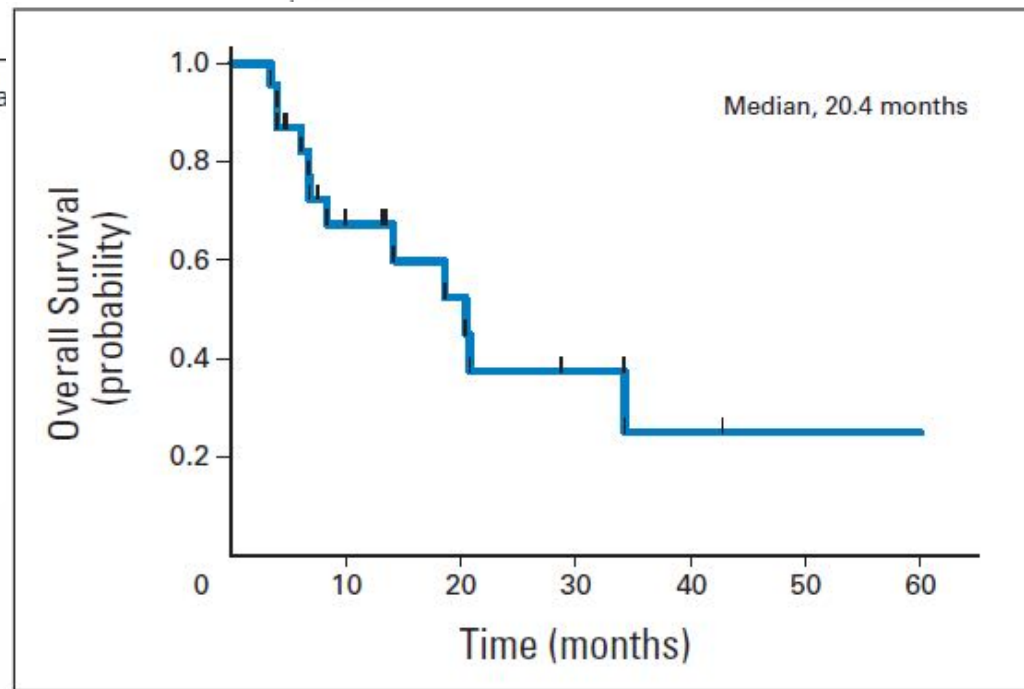


Fig 2. Kaplan-Meier analysis of overall survival (OS) in months for all 24 patients enrolled on the study.

Iyengar et al, J Clin Oncol Dec 2014



[...]

Our study enriched for patients with limited metastatic disease amenable to SBRT, introducing some advantage when comparing our outcomes with those of second-line or maintenance studies with all comers of stage IV NSCLC.

[...]

[...]

Patients with limited metastases may have biology that allows them to have longer survival independent of the success of local or systemic therapies. However, with studies suggesting that 53% of patients that advanced NSCLC would have SBRT-treatable metastases after first-line therapy, a significant proportion of patients could potentially benefit.

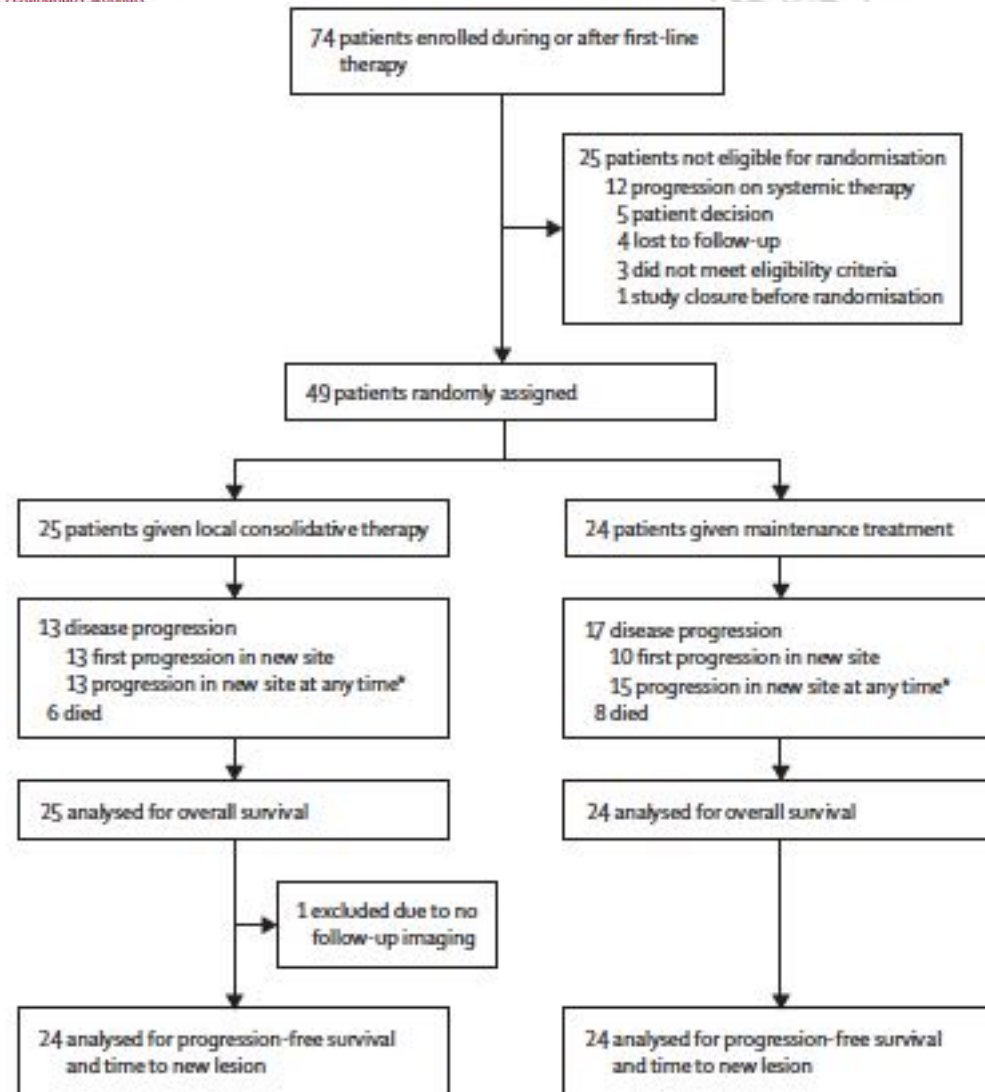
[...]



Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

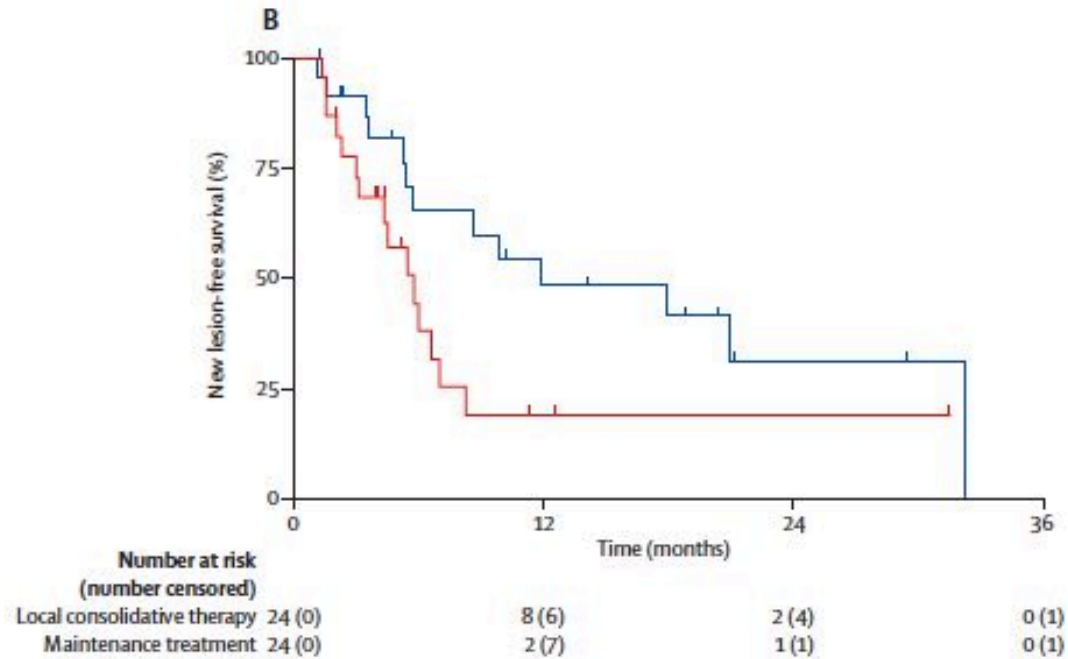
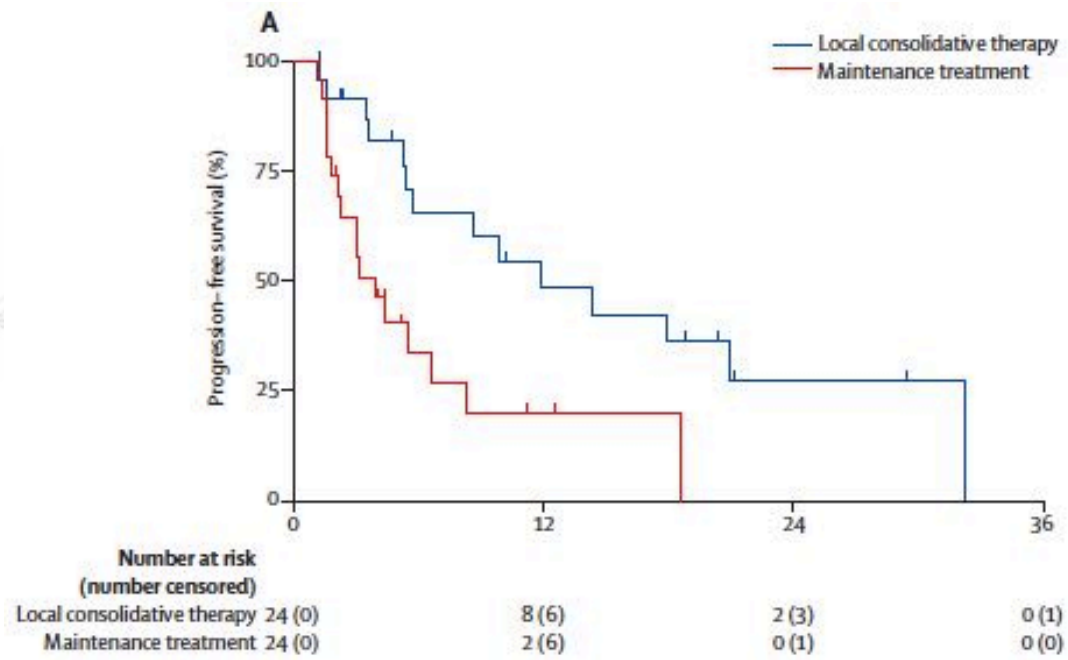
Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Li, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher*, John V He

CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA - VALLE D'AOSTA



Gomez et al, Lancet Oncol 2016

CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VALLE D'AOSTA



Gomez et al, Lancet Oncol 2016

Trattamento locale delle metastasi polmonari

- Quali pazienti considerare eleggibili per il trattamento locale?
- Quale trattamento locale per i pazienti eleggibili?



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