

NEGRAR | Centro Formazione O Ottobre 2018 | IRCCS Ospedale Sacro Cuore Don Calabria

Radioterapia nella malattia metastatica: indicazioni nel 2018?

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





A CONTINUOUS CHANGING: FROM 2D... TO 5 D?







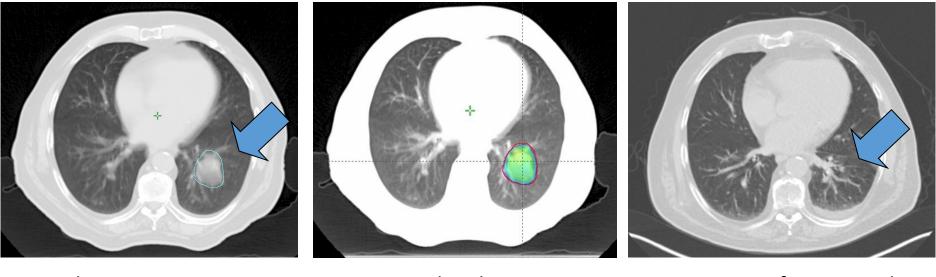
PRECISION DEVISES TO DELIVERY SBRT/SRS

- **3D/4D** target definition on CT slices
- **3D/4D** dose ULTRA-conformation
- Possibility to significantly > doses/<fractions and >LC (SBRT/SABR).
- Better set-up checking (CBCT/EXAC TRAC)
- <toxicity (fit to target conformation by mMLC and ripid gradient by VMAT/IMRT/robotic approach)



LUNG SBRT : EXPERIENCE WITH FFF BEAM ON TRUEBEAM





Planning CT

Dose distribution

Restaging CT after 3 months

50 Gy in 4 fractions with FFF



EARLY STAGE LUNG NSCLC:

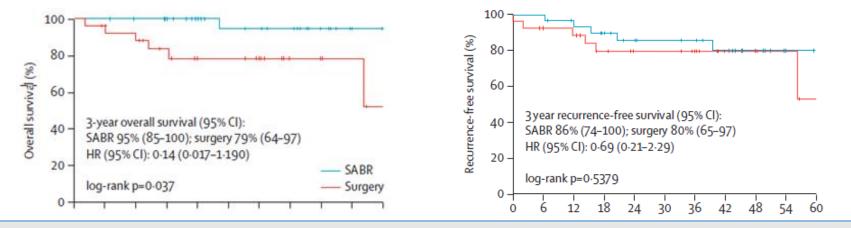
IS SABR EFFECTIVE AS SURGERY?



Lancet Oncol 2015

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang*, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†



The difference in OS between the two groups was statistically significant in favour of SABR.
 No significant differences in of local, regional, or distant metastasis or in RFS between the treatment groups.

Chang et al. Lancet Oncol 2015.







• Early stage NSCLC

Oligometastases and oligorecurrent patients





Is the same the effectiveness of SBRT for the oligometastases?



OLIGOMETASTASES: THE NEW PARADIGMA FOR ABLATIVE DOSES WITH RT

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

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

VOLUME 31 · NUMBER 11 · APRIL 10 2013

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, University of Chicago Medical Center, Chicago, IL



OLIGOMETASTASES: WHAT DEFINITION?



Synchronous oligometastasis uncontrolled primary T	Metachronous oligometastasis uncontrolled primary T > 2 months from cancer diagnosis		
< 2 months from cancer diagnosis			
termi	haustive nology 2018		
Oligorecurrence controlled primary T No systemic therapy ongoing	Oligoprogression controlled primary T Few mts in progression during systemic therapy		



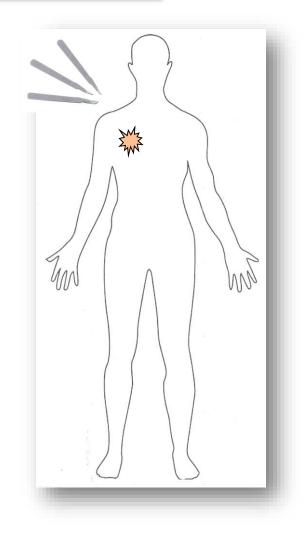
OLIGOMETASTASES: IMPACT OF SURGERY



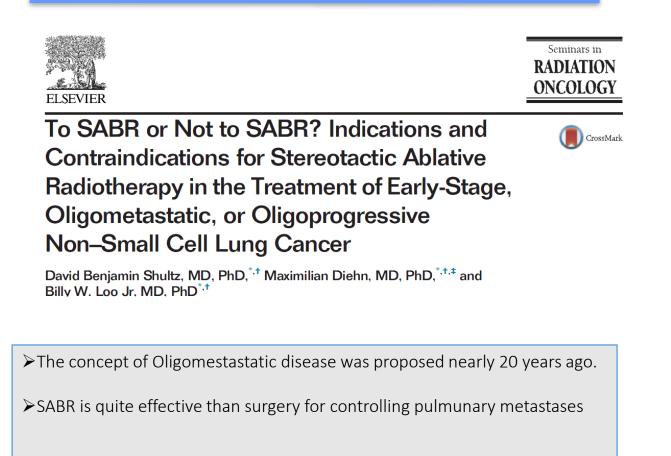
For several anatomical sites, *surgical resection* of metastases prolongs survival in selected patients. *Rubin P, et al. Semin Radiat Oncol,2006*

For example, *surgical resection* is the standard choice for patients with oligometastatic lung cancer.

Unfortunately the benefits of resection and appropriate *selection criteria* in patients who develop metastasis are still poorly defined. *Miller G, et al. J Am Coll Surg, 2007.*

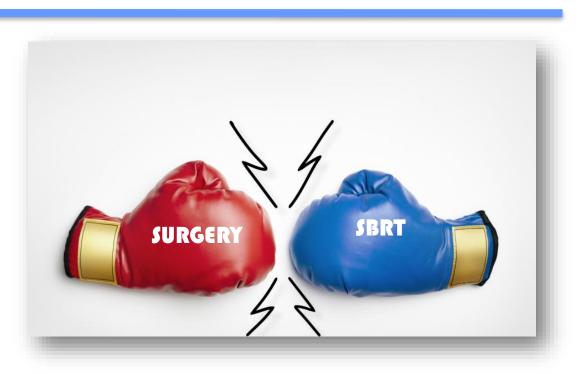








STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS: WHAT ABOUT SBRT VS SURGERY?



NO RANDOMIZED STUDIES

In the absence of randomized studies, it is necessary to compare retrospectives





NCOLOGY

2016

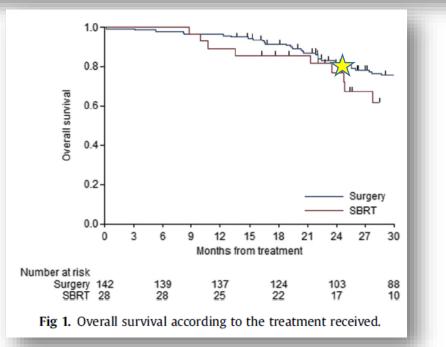
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STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS: WHAT ABOUT SBRT VS SURGERY

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



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.







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†

Journal of Thoracic Oncology® • Volume 9, Number 10, October 2014

Reference	No. of Patients	No. of Targets	Radiation Dose	Median Follow- Up (Months)	Outcomes
Fractionated/Singl	e Fraction SA	ABR			
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 f		90% 2-yr LC, 84% 2-yr OS
Brown et al.25	35	69	•Total doses :24-60 Gy i		77% crude LC, 72.5% 2-yr OS
Rusthoven et al.12	38	63	_{60 Gy/3 fb} •1–3 years LC: 70%–100)%	96% 2-yr LC, 39% 2-yr OS
Wulf et al.24	41	51	30 Gy/3 f •1-2 years OS 48%- 84%	%	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 SA	BR 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





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†

Journal of Thoracic Oncology" • Volume 9, Number 10, October 2014

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
NCT0118563941	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
NCT0172516572	Randomized phase II	Three or less metastases from NSCLC	Consolidative radiotherapy and/or surgery vs. systemic therapy or observation	Progression-free survival

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





Based on published studies, the **patient who could benefit** most from SBRT is the patient with:

- ✓ Disease free interval \ge 12 months,
- ✓ Control of primary tumor,
- ✓ Small lesions,
- ✓ Limited number of lesions (up to three)
- ✓ High dose of radiation 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







Filippo Alongi^{1,2}, Rosario Mazzola¹, Vanessa Figlia¹ and Matthias Guckenberger³

> In summary, SBRT allows a major benefit for lung oligometastatic patients with noncolorectal histology, DFI >24 months, when controlling the primary tumor site, small lesions, and limited number of lesions.



STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS & PET AS PREDICTIVE

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ORIGINAL ARTICLE

Stereotactic Ablative Radiation Therapy for Lung Oligometastases: Predictive Parameters of Early Response by ¹⁸FDG-PET/CT

Rosario Mazzola, MD,^{a,*} Alba Fiorentino, MD,^a Gioacchino Di Paola, MSc,^b Niccolò Giaj Levra, MD,^a Francesco Ricchetti, MD,^a Sergio Fersino, MD,^a Umberto Tebano, MD,^c Stefano Pasetto, MS,^d Ruggero Ruggieri, MS,^a Matteo Salgarello, MD,^d Filippo Alongi, MD^a

^aRadiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy ^bStatistic Sciences Faculty, University of Palermo, Palermo, Italy ^cRadiation Oncology School, University of Padua, Padua, Italy ^dNuclear Medicine, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy

 Table 3. Correlations between Pre-SABR Metabolic Parameters with Local Failure, Distant Metastatic Progression, and Lung

 Metastasis Response

Local Failure (In-Field)			ield)	Distant Metastatic Progression			Lung Metastasis Complete Response (6 mo after SABR)		
Parameter	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
SUV_{max} (for values \geq 5)	2.93	0.52-5.11	0.219	1.98	0.66-5.91	0.221	0.313	0.09-0.99	0.05
SUV_{mean} (for values \geq 5)	1.06	0.22-5.16	0.936	1.85	0.61-5.68	0.281	0.237	0.06-0.84	0.026
MTV	1.01	0.89-1.14	0.855	1.04	0.96-1.14	0.281	1.01	0.91-1.11	0.946
TLG	1.01	0.97-1.02	0.897	1.01	0.99-1.02	0.294	0.99	0.97-1.02	0.791

Note: Boldface indicates statistically significant p values.

SABR, stereotactice ablative radiotherapy; CI, confidence interval; SUV_{max}, maximum standardized fludeoxyglucose F 18 uptake value; SUV_{mean}, mean standardized fludeoxyglucose F 18 uptake value; MTV, metabolic tumor volume, defined as total volume with a standardized uptake value of 2.5 or greater; TLG, total lesion glycolysis.

Conclusions: In the current analysis, complete response from lung metastasis at 6 months after stereotactic body

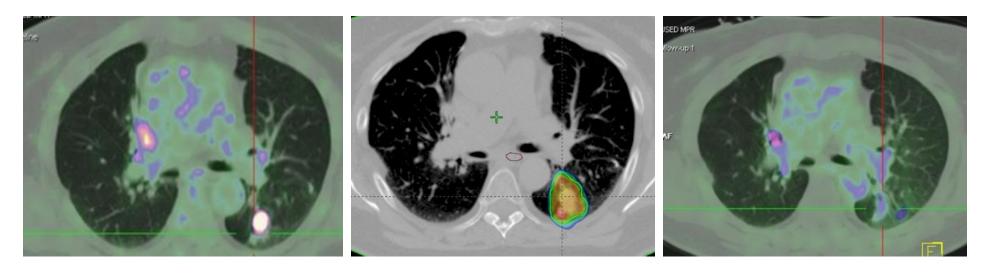
radiation therapy was significantly associated with both the maximum and mean values of pre-SABR ¹⁸FDG-PET/CT SUV. Longer-term trials are strongly advocated to improve the personalization of the monitoring of tumor response in patients with lung oligometastases and, consequently, monitoring of the cost-effectiveness of the health care.



STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS



TRUEBEAM treatment for rectum lung central metastases



PET/CT before SBRT

60 Gy/8 fr. with FFF beams

CR @ 60 days



LUNG OLIGOPROGRESSIVE LESIONS: .. A NEW INDICATION FOR SABR???





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 © Springer-Verlag Berlin Heidelberg 2015 Seminars in RADIATION ONCOLOGY

Semin Radiat Oncol 25:78-86 © 2015



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

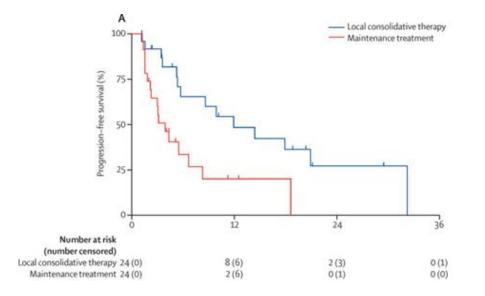
Patients with NSCLC who were treated with targeted agents eventually develop progression owing to the emergence of drug-resistant clones. Because most cancer may retain a drugsensitive genotype, it has been hypothesized that, in this clinical scenario, patients should be maintained on the same targeted 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 only¹¹³ 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

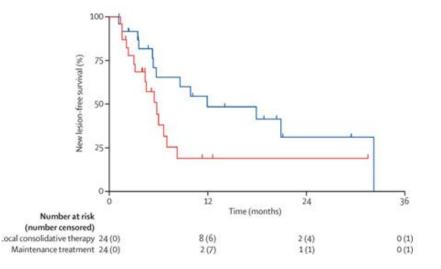


NEW INDICATIONS: SABR AS LOCAL CONSOLIDATIVE THERAPY?

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 Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher*, John V Heymach*





Lancet Oncol 2016; 17: 1672-82





SABR AS LOCAL CONSOLIDATIVE THERAPY : WHICH BED?



Consolidative local therapy in oligometastatic patients

THE LANCET Oncology



question arises: which biologically effective dose would the investigators recommend to reproduce similar findings in actual practice? In the local consolidative therapy group, patients were treated with hypofractionated regimens, as well as stereotactic body radiotherapy, without any specific details in terms of biologically effective dose or schedules of total dose or dose per fraction. Could clinicians assume that a regimen of 30 Gy in ten fractions, as often used for palliation,² is as effective as ablative radiotherapy doses? If so, the real impact of the biologically effective dose and dose-effectiveness relationships should be totally revised with readers taking a more sceptical view. In the

Filippo Alongi, Rosario Mazzola, Francesco Ricchetti rosariomazzola@hotmail.it

Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar, Italy

Lancet Oncol 2016; 17: 1672-82



SABR AS LOCAL CONSOLIDATIVE THERAPY : UPDATE FROM ASTRO

Consolidative local therapy in oligometastatic patients

ASTRO



Aggressive treatment for some stage IV lung cancer patients can dramatically improve overall survival

Adding radiation therapy or surgery to systemic therapy for stage IV lung cancer patients whose cancer has spread to a limited number of sites can extend overall survival time significantly, according to new results from a multicenter, randomized, controlled phase II study. Researchers previously reported encouraging results for progression-free survival (PFS), which were published in Lancet Oncology in 2016. These new results were presented as the abstract, Local consolidative therapy (LCT) improves overall survival (OS) compared to maintenance therapy/observation in oligometastatic non-small cell lung cancer (NSCLC): Final results of a multicenter. randomized, controlled phase 2 trial by Daniel Gomez, MD, Associate Medical Director of radiation oncology at the University of Texas MD Anderson Cancer Center in Houston.

MD Anderson Cancer Center in Houston.



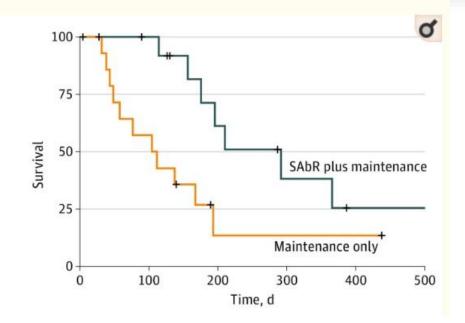


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NEW INDICATIONS: SABR AS LOCAL CONSOLIDATIVE THERAPY?







Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone, with no difference in toxic effects.



SABR BEFORE TO DELAY NEW LINE OF SYSTEMIC THERAPY : A NEW INDICATION?

Medical Oncology (2018) 35:121 https://doi.org/10.1007/s12032-018-1190-8

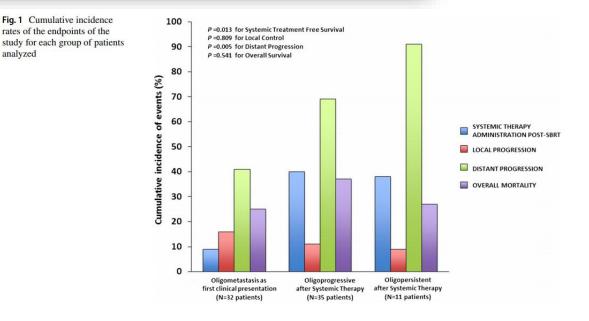
ORIGINAL PAPER

Stereotactic body radiotherapy for lung oligometastases impacts on systemic treatment-free survival: a cohort study

Rosario Mazzola¹ · Sergio Fersino¹ · Giuseppe Ferrera² · Giovanni Targher³ · Vanessa Figlia¹ · Luca Triggiani⁴ · Nadia Pasinetti⁴ · Antonio Lo Casto⁵ · Ruggero Ruggieri¹ · Stefano Maria Magrini⁴ · Filippo Alongi^{1,6}

analyzed

- Seventy-eight patients and 114 lung metastases were analyzed (oligorecurrence, oligoprogressive disease, oligopersistent disease).
- In the present experience, SBRT allowed to delay the administration of systemic treatments in several settings of lung oligometastasis.



CrossMark





SBRT LUNG OLIGOMETASES/OLIGOPROGRESSIVE: CONCLUSIONS



•The perfect candidate to Local treatment in case of oligometasases is to establish

•Results suggest that SABR for LUNG metastases may provide durable infield control.

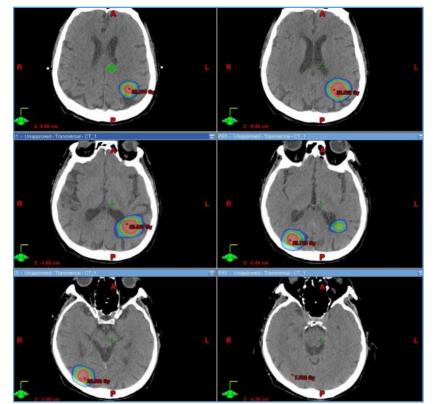
•These outcome results appear equivalent to those achievable with surgery.

•In Selected oligoprogressive setting, local therapy, including SBRT could add impact on outcome compared to drug maintaince alone.



BRAIN METASTASIS: A CHALLENGING ISSUE IN CANCER TREATMENT STRATEGY

- Given systemic therapy advancements, patients live longer and approximately 20-40% of new cancer patients will develop brain metastases.
- In brain solitary metastasis, or oligometastatic setting, SRS has been considered a primary option as well as surgery.
- ✓ For multiple metastases(>3-4), WBRT has been considered the standard of care and it can only increase survival between 3 and 6 months.







NEW «CLINICAL» OPTIONS FOR INTRACRANIAL RADIOSURGERY?

WBRT is really the optimal choice for >3-4 mts??

Stereotactic radiosurgery for patients with multiple brain \Rightarrow i (JLGK0901): a multi-institutional prospective observational study Lancet Oncol 2014; 15: 387-95

•**M&M**: 1194 pts treated with SRS $(1 \rightarrow 10 \text{ brain mets})$

•RESULTS: Overall survival → 2-4 BM= 5-10 BM

Interpretation Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.

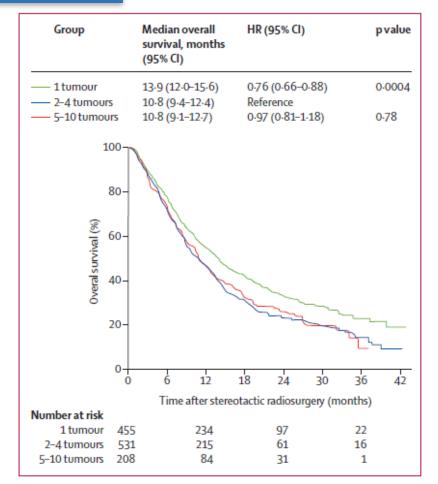
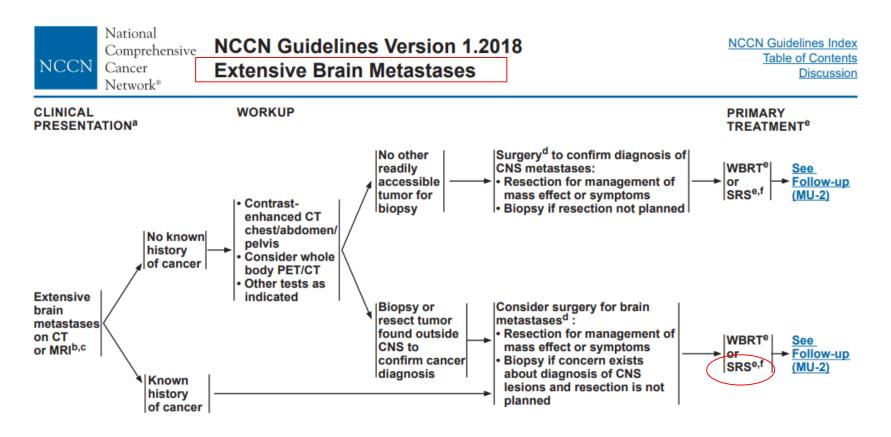


Figure: Kaplan-Meler curves of overall survival HR=hazard ratio.





NEW «CLINICAL» OPTIONS FOR INTRACRANIAL RADIOSURGERY



eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

fSRS can be considered for patients with good performance and low overall tumor volume and/or radioresistant tumors such as melanoma. (Yamamoto M, Serizawa

T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)

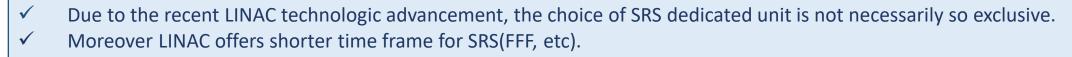




CONVENTIONAL «TECHNOLOGICAL» OPTIONS FOR INTRACRANIAL RADIOSURGERY

Stereotactic radiosurgery for intracranial metastases: linac-based and gamma-dedicated unit approach

Filippo Alongi, Alba Fiorentino, Pietro Mancosu, Pierina Navarria, Niccolò Giaj Levra, Rosario Mazzola & Marta Scorsetti



	GK	Linac Intracranial and extracranial		
Sites treated	Intracranial only			
On-board image	No: for A,B, C, PFX models Yes: for Icon model	Yes		
Immobilization	Frame: for A, B, C, PFX models Frameless: for Icon model	Frame and frameless		
SRS time	30–60 min	20–30 min for conical collimator 10–15 min for flattening filter delivered <2 min for flattening filter Free delivered		
Fractionated therapy	Available only with GK Icon models	Yes		
Field shaping	Conical collimators	Conical collimators and MLC		
Multipurpose machine	Intracranial SRS only	SRS, SRT, 3D RT, IMRT, IGRT, electron RT, gated RT, conformal arc therapy		

MLC: Multi-leaf collimator; GK: Gamma Knife; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; Linac: linear accelerator.



2016

REVIEW

OF ANTICANCER THERAPY

Alongi et al et al. Expert review anticancer Therapy 2016



SRS/SFRT for multiple brain metastases:

First worldwide experience and clinical results using HyperArc: EVALUATION@ 6 Months OF THE FIRST 43 PTS (246 LESIONS)

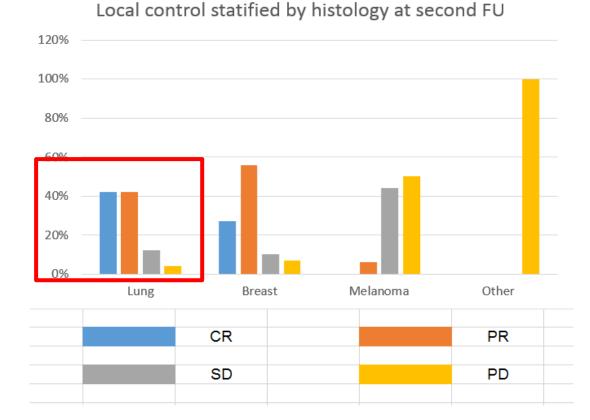


Results

PREDICTOR FACTOR for Local Control

Analysis of predictor factors for LC by histology

Histology	CR	PR	SD+PD	P value
Lung cancer	16%	49%	35%	
Breast cancer	30%	43%	27%	0.0001
Melanoma	0%	32%	68%	0.0001
Other	18%	30%	52%	





2017

OF ANTICANCER THERAPY

SBRT LUNG OLIGOMETASES/OLIGOPROGRESSIVE:

WHAT ABOUT NEW DRUGS INTERACTIONS?



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)

In the setting of oligometastatic and oligoprogressive disease, new molecules demonstrated to be safe and effective, opening to a promising and emerging application of the best interaction between new drugs and new modalities of radiotherapy with the goal to postpone an alternative chemotherapy line, but clinical trials are necessary.





FUTURE OR....COMING SOON IN PRACTICE:

PROTON THERAPY?HEAVY IONS?

BIOLOGICAL PROFILING BEFORE RT?

WHICH INTERACTIONS WITH NEW DRUGS??