

II INCONTRO DI AGGIORNAMENTO SCIENTIFICO DIPARTIMENTO ONCOLOGICO

“TRATTAMENTO del NSCLC IV STADIO: Ruolo della radioterapia”

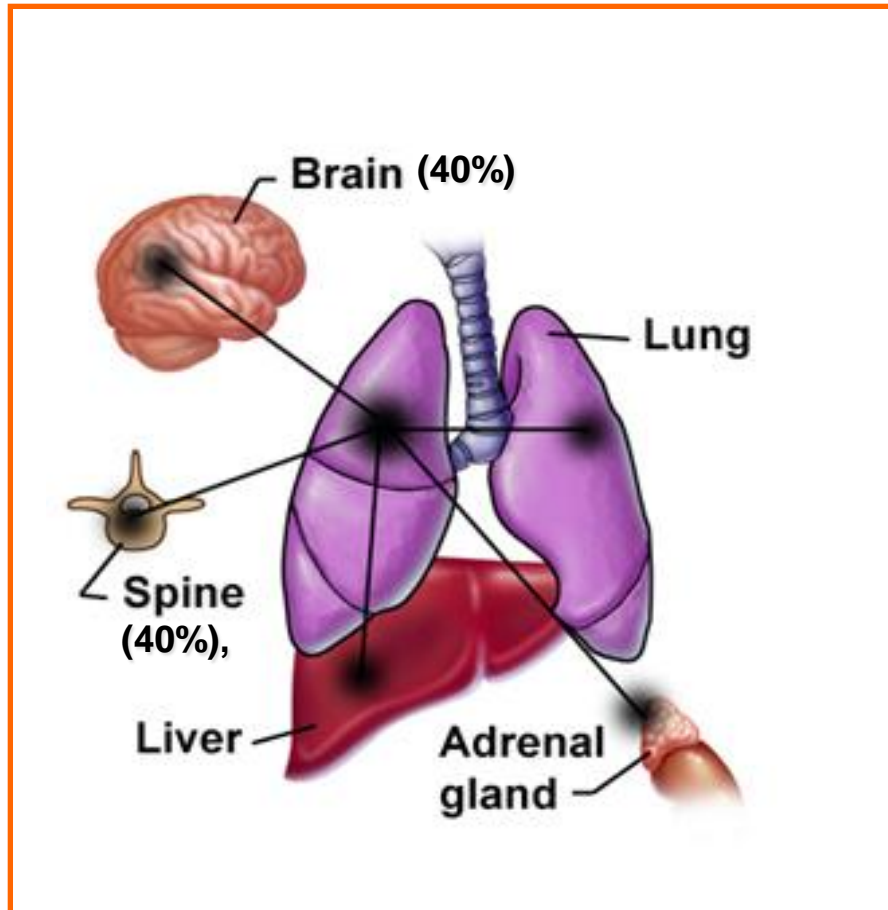
FILIPPO ALONGI

Direttore UOC Radioterapia Oncologica



Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

NATURAL HISTORY OF NSCLC SPREAD



BRAIN METASTASES



Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

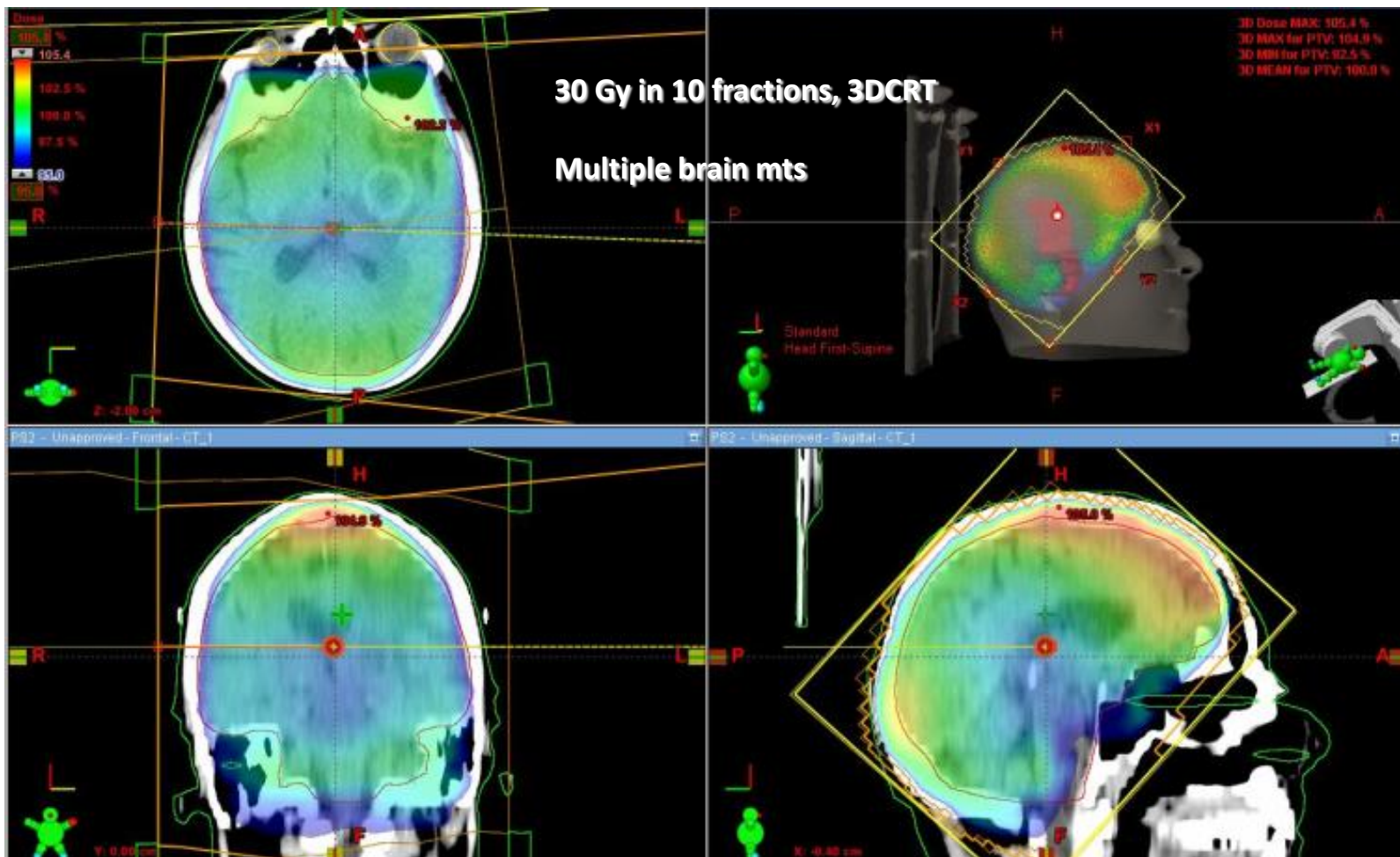
PALLIATIVE/SYMPHTOMATIC WHOLE BRAIN RADIOTHERAPY

- **WBRT (WHOLE BRAIN RADIOTHERAPY)** is considered the standard treatment for patients with **multiple** brain metastasis.
- Important role in **postoperative management** of patients who have undergone surgical excision.
- It may **prevent or delay** the progression of **neurological deficit**, restore funtion and decrease steroid dependency.
- A dose of **30 Gy in 10 fractions** or **20 Gy in 5 fractions** is recommended.
- However ... the survival is poor.

Biswas et al. J Cancer Res Ther. 2006



PALLIATIVE/SYMPHTOMATIC WHOLE BRAIN RADIOTHERAPY





Contents lists available at [ScienceDirect](#)

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature



Allison Ashworth, George Rodrigues, Gabriel Boldt, David Palma*

Department of Radiation Oncology, London Regional Cancer Program, London, Canada

- Surgical metastatectomy was the most common ablative technique for oligometastases (55% of studies).
- Stereotactic radiosurgery (SRS) for brain metastases and SABR were used in 35% and 10% of studies, respectively



Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

RADIOSURGERY : CAN WE IMPROVE RESULTS?

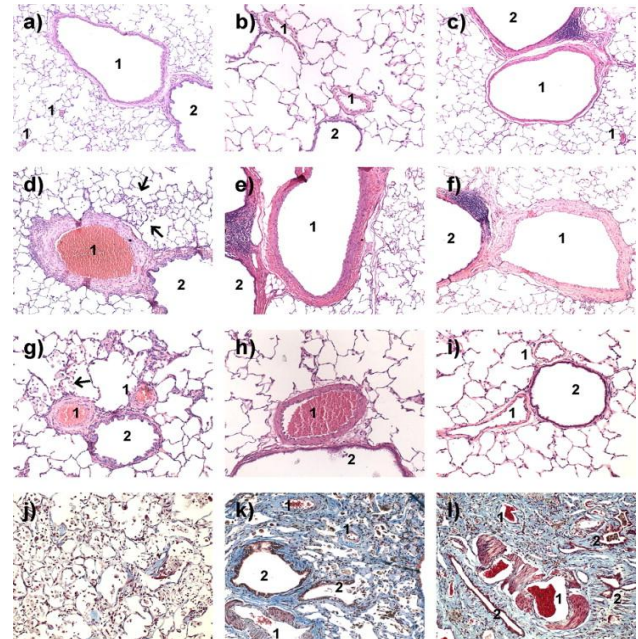
•In terms of **Radiobiology**, **RADIOSURGERY** may add a novel mechanism of radiation-induced damage.

•At higher doses per fraction (**ablative doses**), emerging data suggest that, in addition to direct cytotoxicity, a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill.

Garcia - Barros M., et al. Science, 2003

Targeting the tumor vasculature for obliteration with high-dose radiation may be beneficial for tumor control.

Fuks and Kolesnick, Cancer Cell 2005 .



STEREOTACTIC RADIOSURGERY



Non-Invasive



Invasive



RADIOSURGERY FOR SINGLE/FEW BRAIN

- NO randomized trials comparing surgical metastasectomy with SRS
- → Retrospective reports support comparable outcomes.
- The SELECTION of treatment should depend on patient- and disease-related factors (**SIR/RPA**).

Radiosurgery is intended to provide:

- > local tumor control,
- improve clinical symptomatology,
- enhance survival.

All of these radiosurgical goals are generally achieved with:

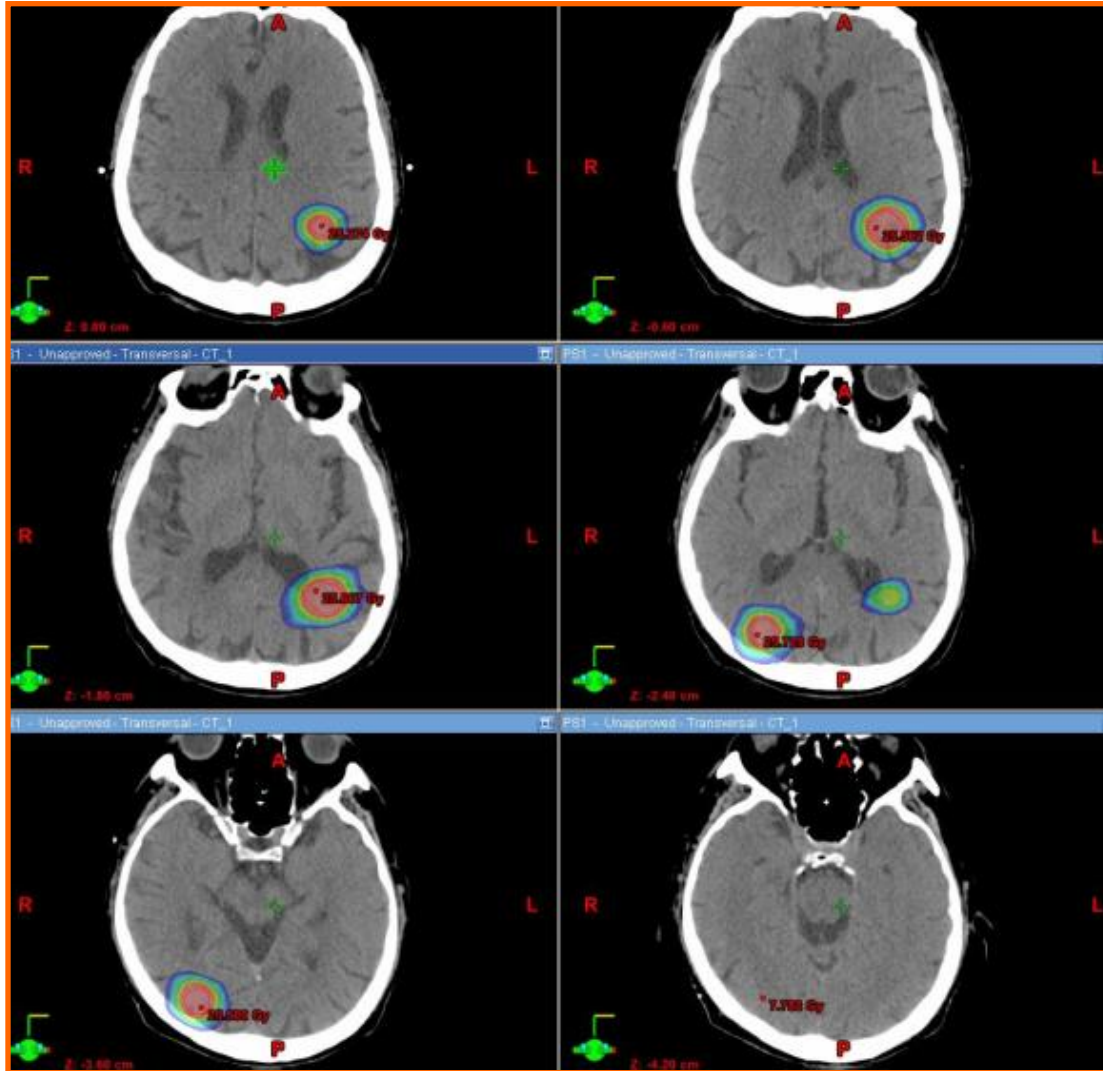
- low morbidity,
- low cost,
- essentially zero mortality

*Noyes et al, Radiosurgery 1996;
Rutigliano et al, Neurosurgery 1995*

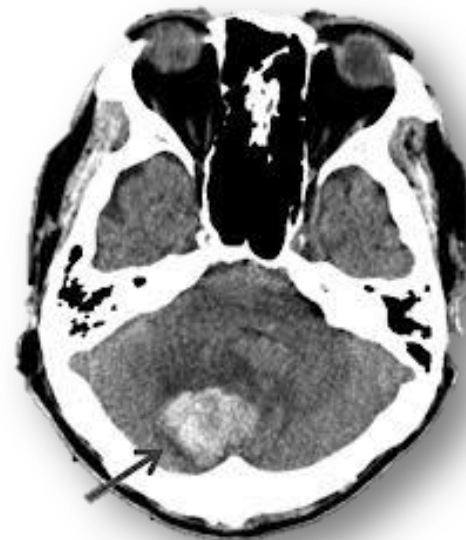
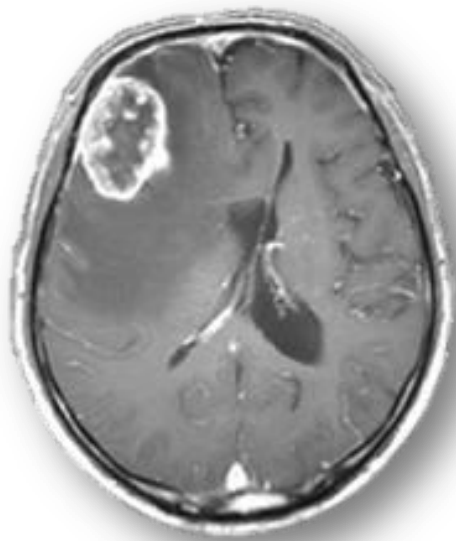
RADIOSURGERY FOR SINGLE/FEW BRAIN METASTASES

*Patient with 2
brain metastases.*

RADIOSURGERY:
*Dose prescription:
25 Gy in single
fraction.*



FRACTIONATED STEREOTACTIC RADIOSURGERY



Lesion diameter >3 cm

- 3 FRACTIONS (>8 Gy per fraction)
- 2 FRACTIONS (> 11.5 Gy per fraction)

Wiggenraad R, et al. A systematic review. *Radiother Oncol* 2011



Brain metastases:

***SRS vs SRS + WBRT
randomized clinical trials***

Courtesy of Dr. E. Maranzano, Terni

Randomized phase III trials in brain metastases

SRS vs SRS + WBRT:

	# of patients	Intracranial progression free survival (months)	Overall survival (months)
<i>Aoyama 2006</i>	132 (67 SRS vs 65 SRS+WBRT)	Favour to SRS + WBRT	No difference
<i>Chang 2009</i>	58 (30 SRS vs 28 SRS+ WBRT)		
<i>Kocher & Soffiatti 2010</i>	359 (179 SRS/Surg. vs 180 SRS/Surg + WBRT)		
<i>Mondschein 2010</i> (Abst ASTRO) <i>MELANOMA</i>	74 45 SRS vs 29 SRS+WBRT	2.1 vs 3 ($p = 0.815$)	

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

- 1. WBRT causes a decline in learning and memory function by 4 months compared with the group that received SRS alone.**
- 2. In patients 1-3 brain metastases initial treatment should be SRS**
- 3. clinical close monitoring is recommended for early diagnosis of relapse**
- 4. WBRT should be reserved only as a salvage therapy**

CAN TECHNOLOGY HELP US? May be,,,



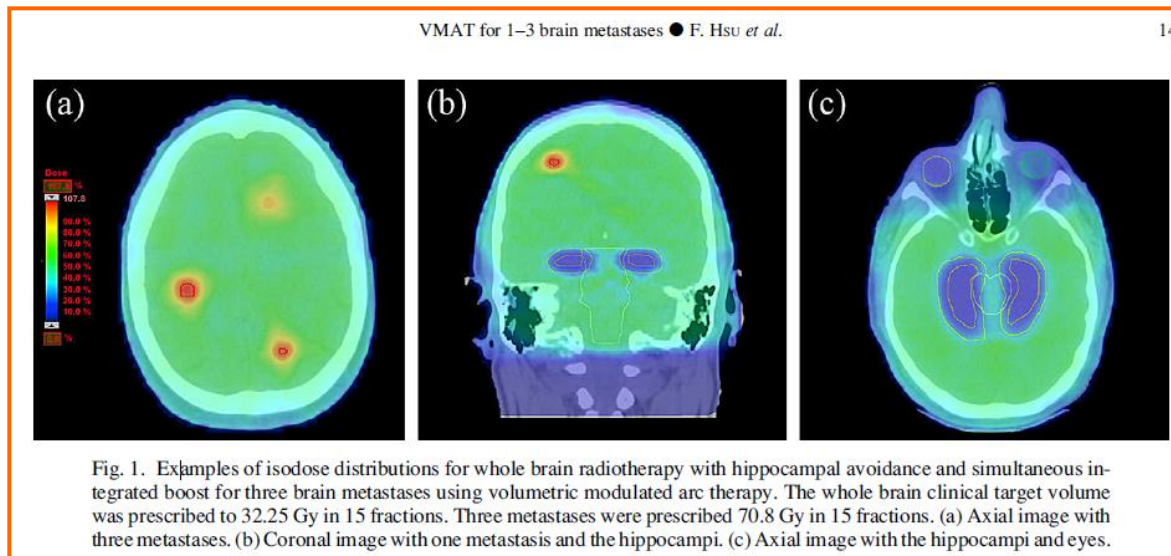
CLINICAL INVESTIGATION

Brain

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUS INTEGRATED BOOST FOR 1–3 BRAIN METASTASES: A FEASIBILITY STUDY USING VOLUMETRIC MODULATED ARC THERAPY

FRED HSU, M.D.,* HANNAH CAROLAN, M.D.,† ALAN NICHOL, M.D.,* FRED CAO, PH.D.,‡
NIMET NURANEY, R.T.T.,† RICHARD LEE, PH.D.,§ ERMIAS GETE, PH.D.,§ FRANCES WONG, M.D.,†
MOIRA SCHMULAND, M.Sc.,§ MANRAJ HERAN, M.D.,¶ AND KARL OTTO, PH.D.‡

hippocampal avoidance



CAN TECHNOLOGY HELP US?

May be,, for multiple metastases(from 3 to 5) when WBRT alone could be too poor

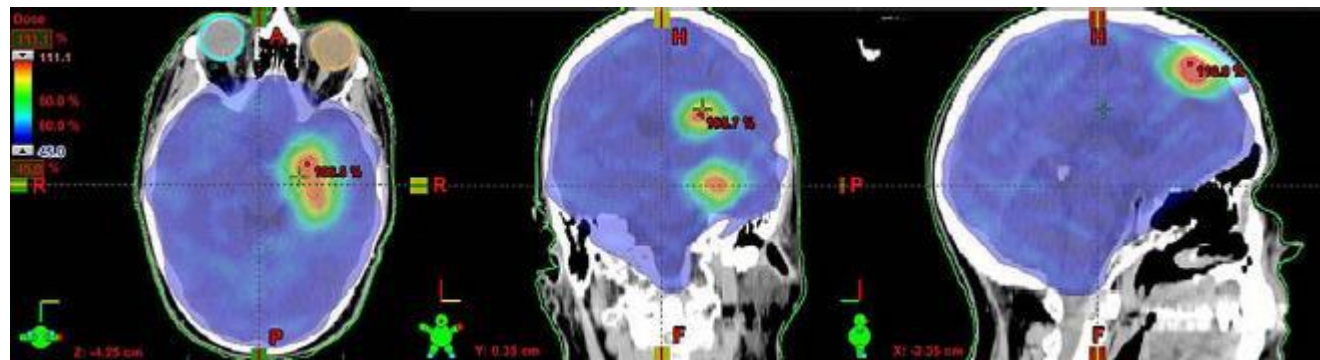


PHYSICS CONTRIBUTION

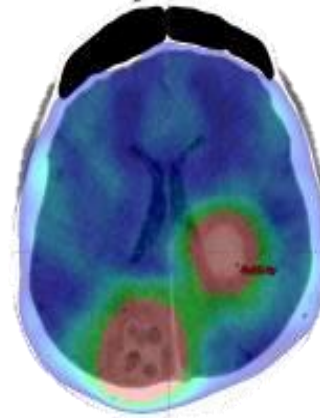
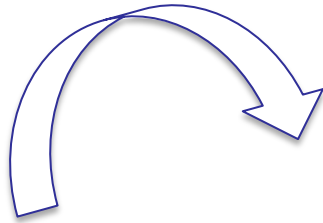
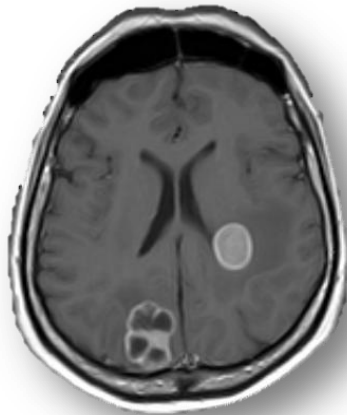
WHOLE-BRAIN RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST TO MULTIPLE BRAIN METASTASES USING VOLUMETRIC MODULATED ARC THERAPY

FRANK J. LAGERWAARD, M.D., PH.D., ELLES A. P. VAN DER HOORN, WILKO F. A. R. VERBAKEL, PH.D., CORNELIS J. A. HAASBEEK, M.D., BEN J. SLOTMAN, M.D., PH.D., AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.

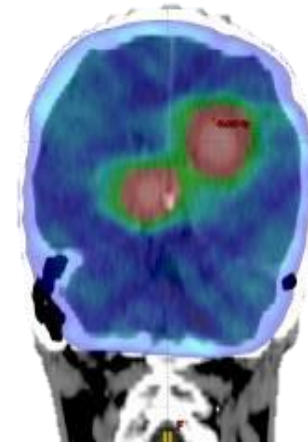
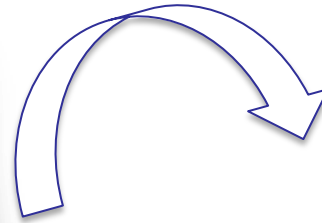
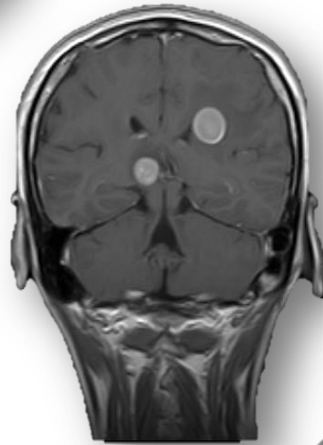
Delivery of integrated plans of WBRT and boosts to multiple brain metastases



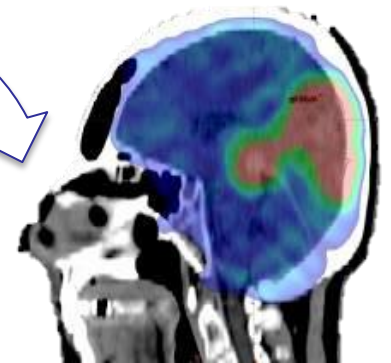
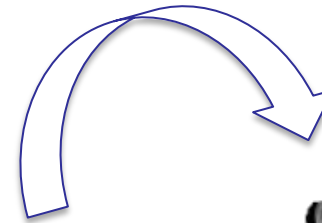
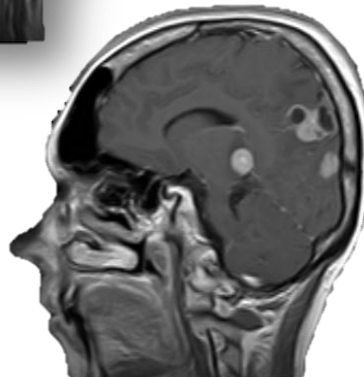
Brain Metastases and Simultaneous boost



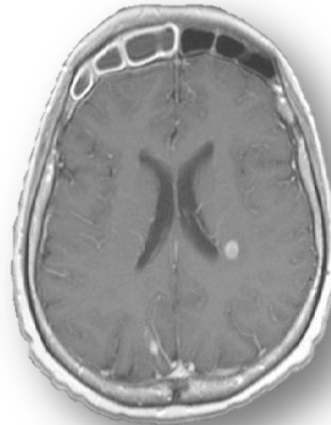
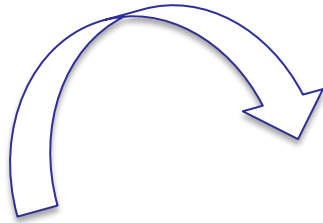
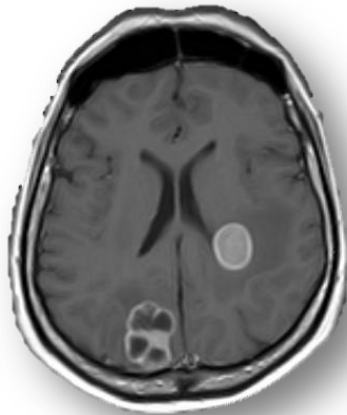
**SIB:
WBRT 30Gy/40Gy**



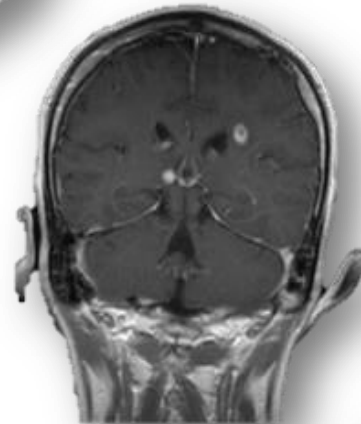
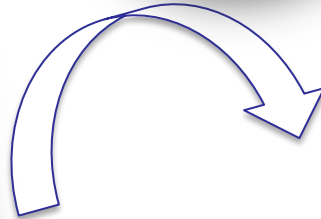
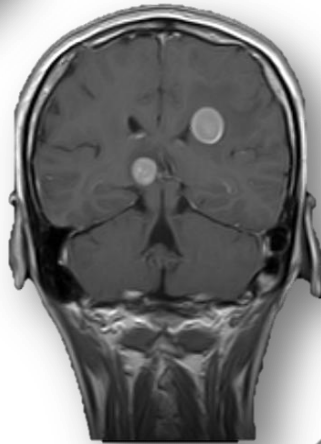
**Pz. 35 y.
4 metastases**



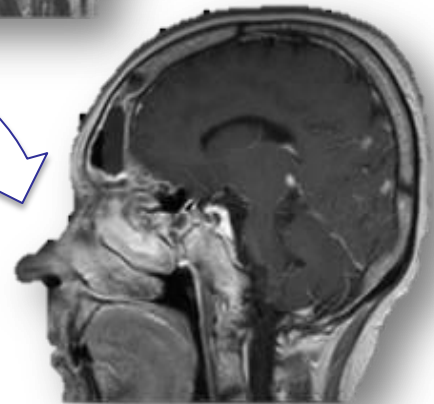
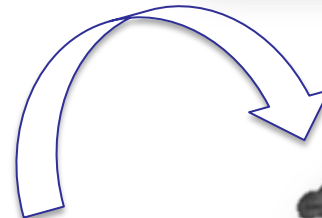
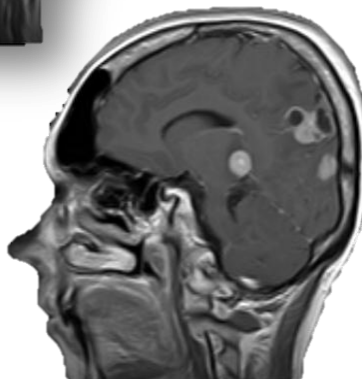
Brain Metastases and Simultaneous boost



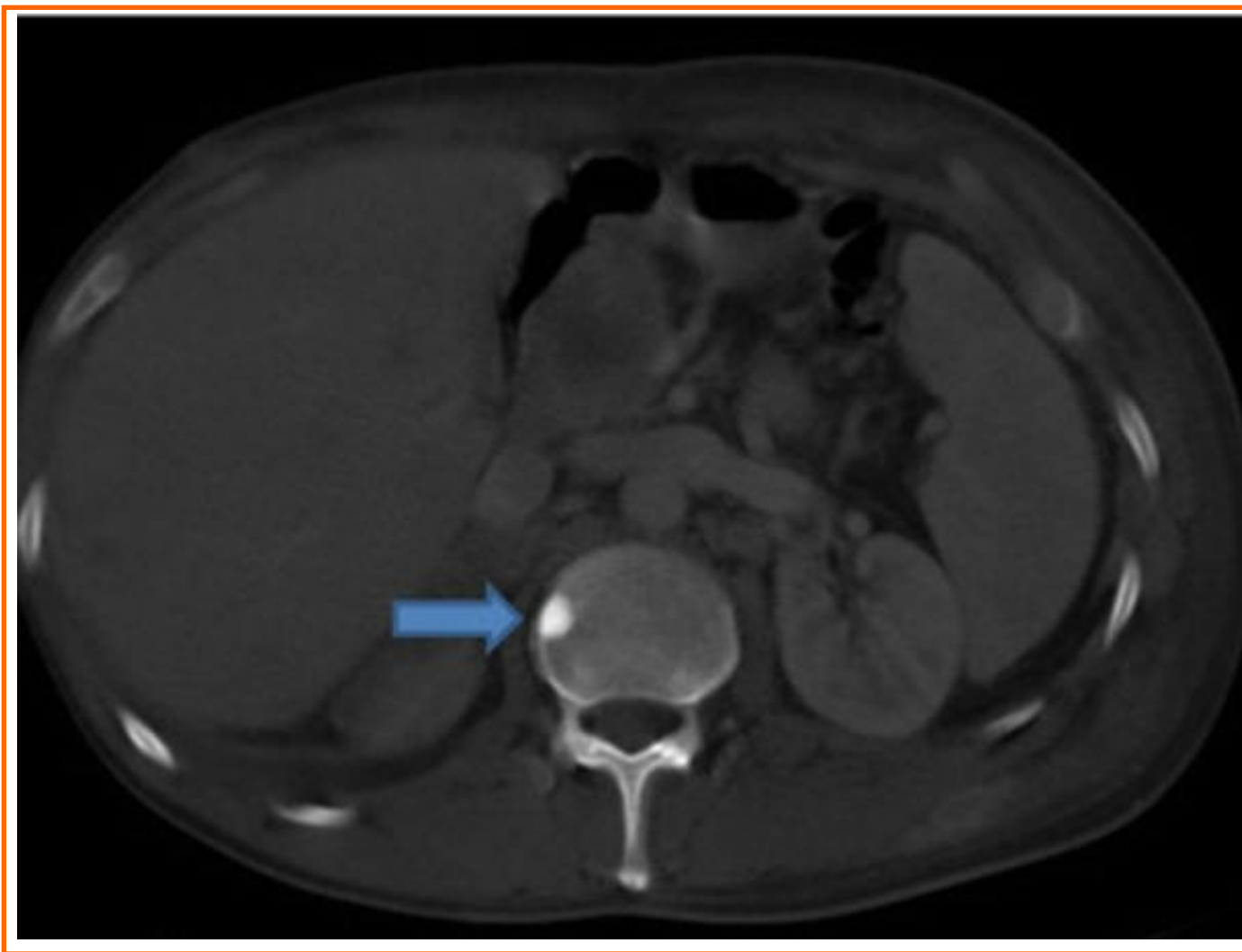
MRI after 3 months



**Pz. 35 y.
4 metastases**



BONE METASTASES



Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)

PALLIATIVE/SYMPHTOMATIC BONE RADIOTHERAPY

Primary Outcomes in Studies of RT and Metastatic RCC

Study ^a	Objectives	No.	Dose in (Gy)	Response rate	Dose response
Retrospective institutional studies					
Fossa et al., 1982 ⁴	Subjective/objective response	27	30-40	84% subjective 50% objective	NA
Seitz et al., 1988 ⁵	Subjective/objective response	45	20-50	58% subjective 18% objective	NA
Studies of dose vs. response relation					
Halperin and Harisiadis, 1983 ⁶	Symptom relief vs. TDF	35	20-60	77% bone 30% neuro	No
Onufrey and Mohiuddin, 1985 ⁷	Symptom relief vs. TDF	125	20-60	25% TDF < 70 65% TDF > 70	Yes
DiBiase et al., 1997 ⁸	Palliative response and BED ₁₀	107	8-64	86% overall 49% complete	Yes
Wilson et al., 2003 ⁹	BED _{3,7} vs. time to disease progression, response	78	4-55	73% overall 6% complete	No
Prospective studies					
Brinkmann et al., 1999 ¹⁴	Combined RT and chemo-immunotherapy	12	40-55	33% CR 8% PR	NA
Redman et al., 1998 ¹⁵	Combined RT and IL-2	16	16	13% PR	NA
Huguenin et al., 1998 ¹⁶	Palliative end points in RCC and melanoma	90	6-40	56% pain 36% neuro	NA

RT: radiotherapy; RCC: renal cell carcinoma; Gy: gray; NA: not applicable; TDF: time dose fractionation; neuro: neurologic response; BED₁₀: biologic effective dose; CR: complete response; PR: partial response; IL-2: Interleukin-2.

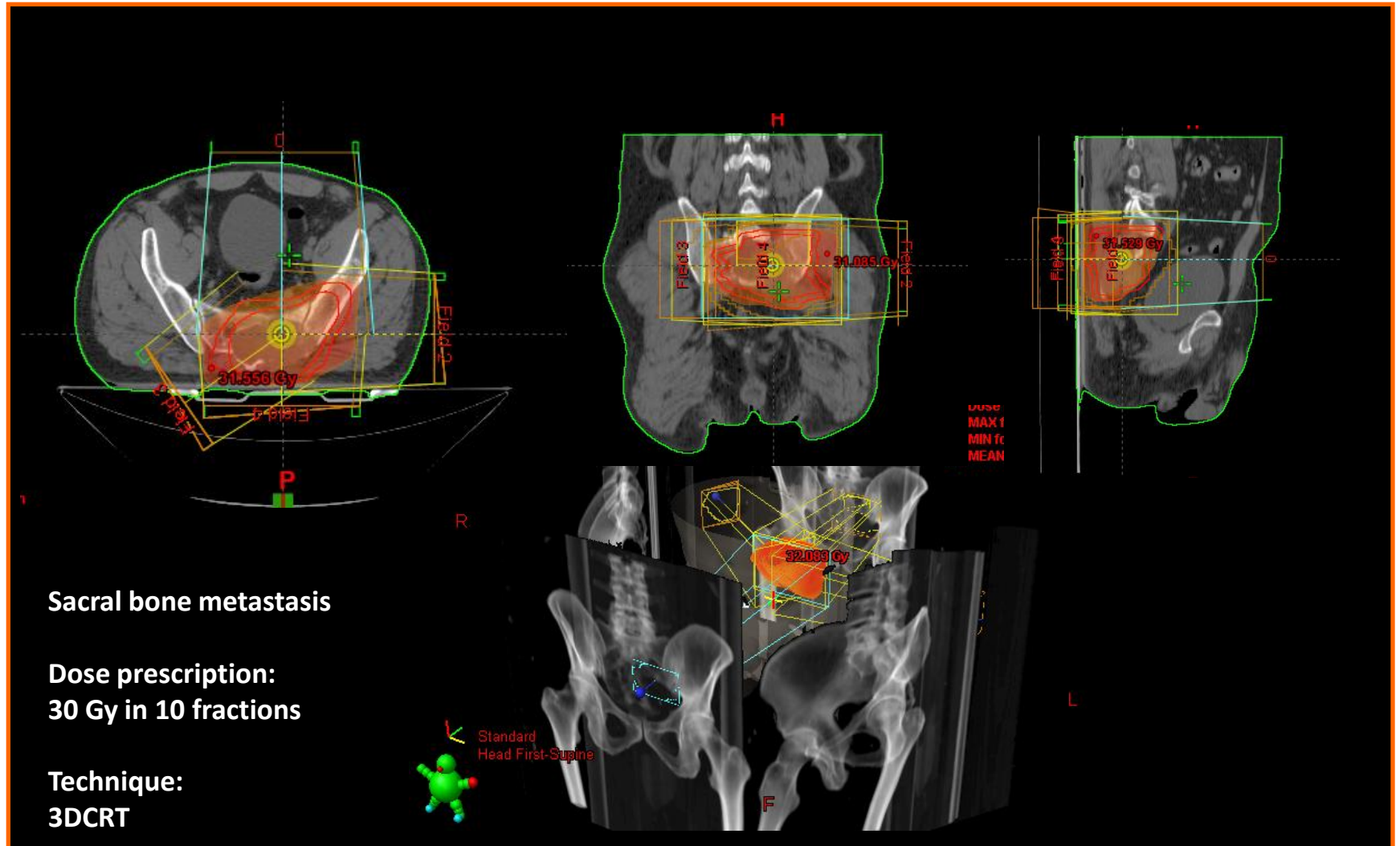
^a Studies of brain metastases from renal cell carcinoma not included.



• In a prospective phase II study using validated quality of life questionnaires, Lee et al. from the Princess Margaret Hospital demonstrated that 83% of patients treated for pain had experienced significant pain relief with 30 Gy radiation delivered in 10 fractions. (Lee, *Cancer* 2005).



PALLIATIVE/SYMPHTOMATIC BONE RADIOTHERAPY





STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT)

- The primary end point of **SBRT** is to achieve local control of targeted tumor deposits with *ablative* doses.
- In general SBRT for oligometastases should follow the same philosophy relating to indications for surgical metastasectomy.
- As smaller foci of metastases are found, high conformal radiation may well prove *less invasive and more/equal effective* than surgery, decreasing morbidity and delivering ablative treatment more economically on an outpatient basis.

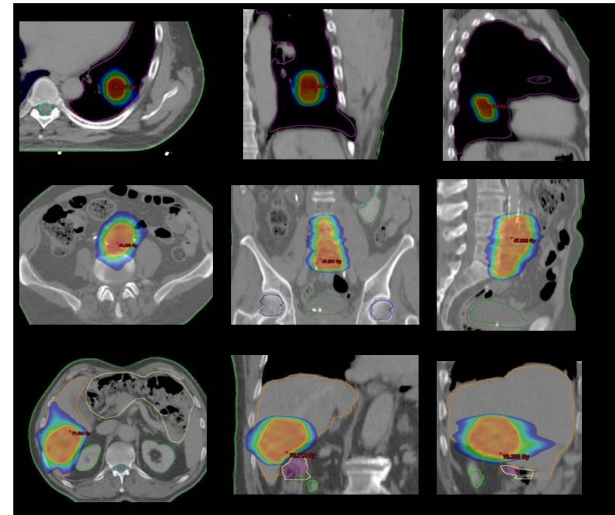
Alongi F et al. Critical Rev Oncol Hematol, 2012

The
Oncologist®

Radiation Oncology

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



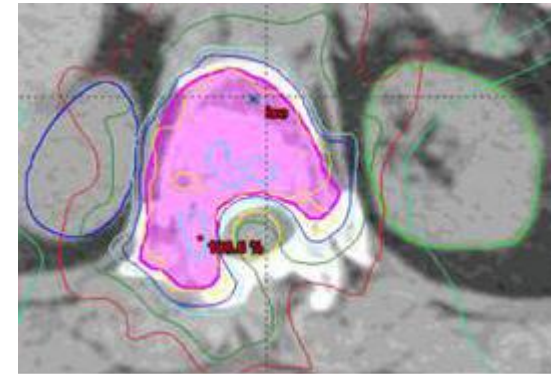


STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT): SPINE METASTASES

Table 5. Summary of published trials of stereotactic body radiation therapy for spinal metastases

Study	n of patients	Median dose/ n of fractions	Median follow-up, mos	Local control rate	Pain response
Yamada et al. [73]	93	24 Gy/1	15	15-mo, 90% (imaging)	NS
Ryu et al. [74]	49	10–16 Gy/1	6.4	93% (imaging and pain)	85%
Sahgal et al. [56]	14	24 Gy/3	9	78% (imaging and/or pain)	NS
	25	24 Gy/3	7	92% (imaging and/or pain)	NS
Nguyen et al. [75]	48	30 Gy/5 24 Gy/3	13.1	78% (imaging)	52%
Tsai et al. [76]	69	15.5 Gy/2	10	10-mo, 96.8% (imaging)	Improved pain control, 88%
Chang et al. [58]	63	30 Gy/5 27 Gy/3	21.3	77% (imaging)	Narcotic use declined 60% to 36%
Gibbs et al. [77]	74	14–25 Gy/1–5	9	NS	Clinical benefit, 84%
Gerstzen et al. [78]	393	20 Gy/1	21	88% (imaging)	Clinical benefit, 86%

Abbreviation: NS, not significant.



- Local control based on imaging and/or pain control is achieved in 80% of presentations
- There are several dose prescription schedules and total doses or doses per fraction, making direct comparison difficult, with a follow-up time globally of a few months.
- The predominant pattern of failure after SBRT for spinal metastases is characteristic of the procedure because the principle of SBRT is to treat only the target region, and areas close to the spinal cord are frequently underdosed.



STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT): LUNG METASTASES

Alongi, Arcangeli, Filippi et al.

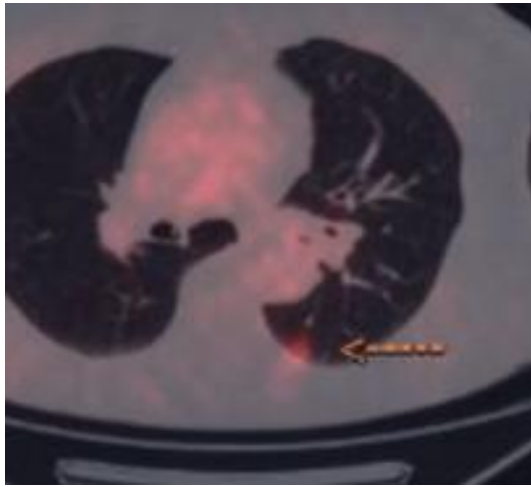
3

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

Study	n of patients	Median dose/n 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 \geq 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%)

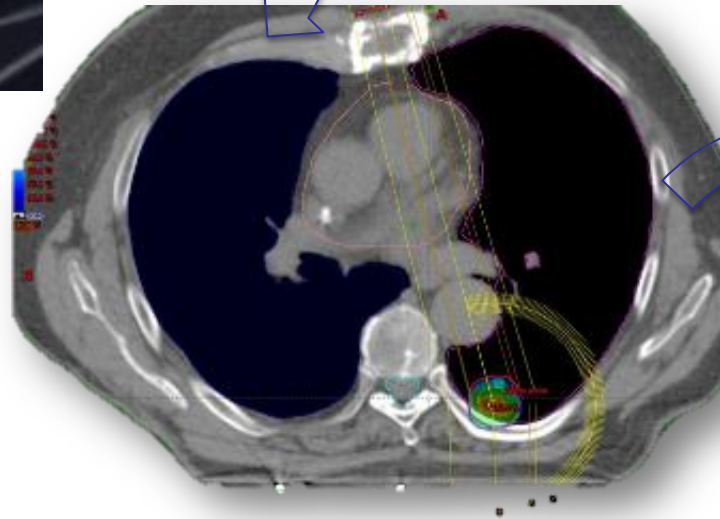
...the high local control rates and potential survival benefits- without significant side effects- justify the use of SBRT as an alternative to surgery.

STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT): LUNG METASTASES



Pre SBRT

TRUEBEAM treatment for melanoma
isolated lung metastasis



CR @ PET after 48 Gy in 4
fractions with FFF beams

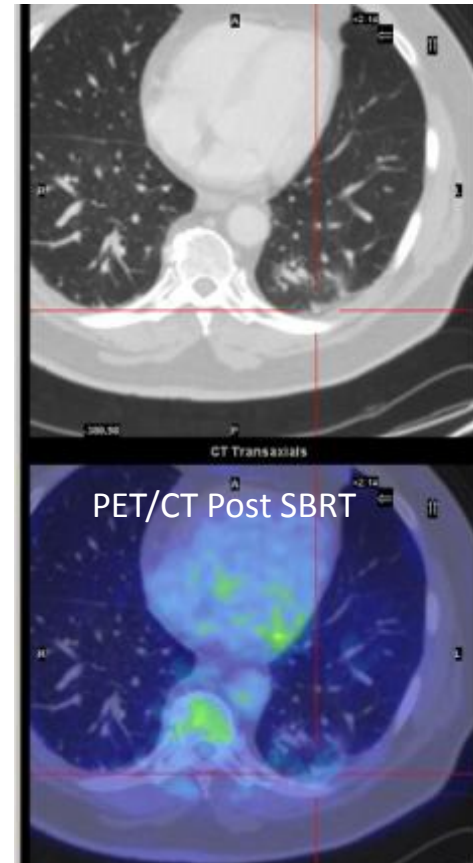
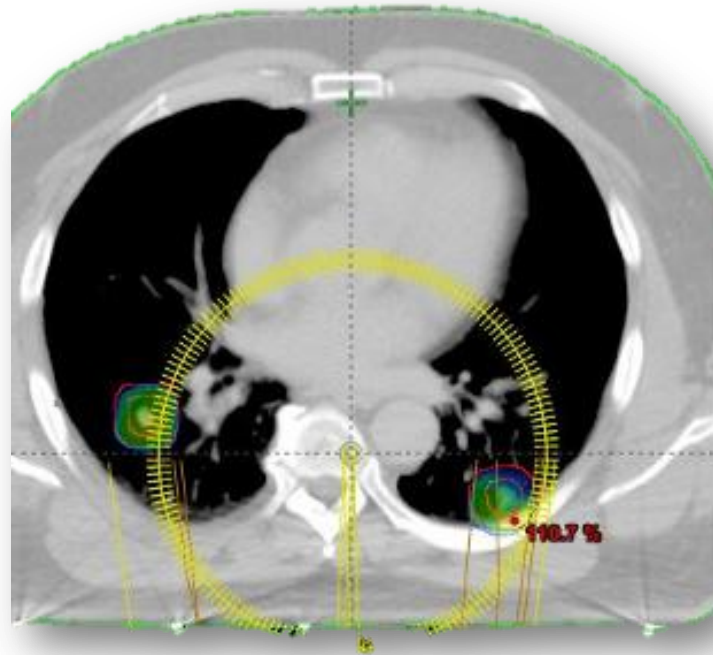
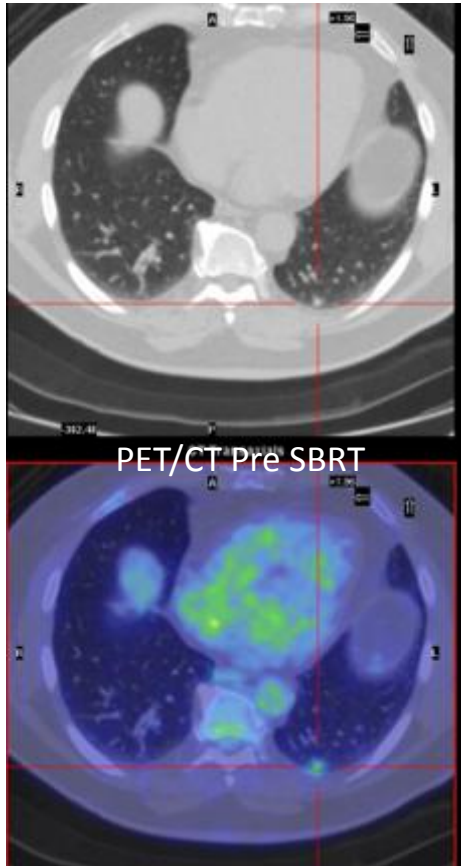


Post SBRT

STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT):

LUNG METASTASES

TRUEBEAM treatment for rectum bilateral lung metastases



CR @ PET/TC after 48 Gy in 4 fr. with FFF beams

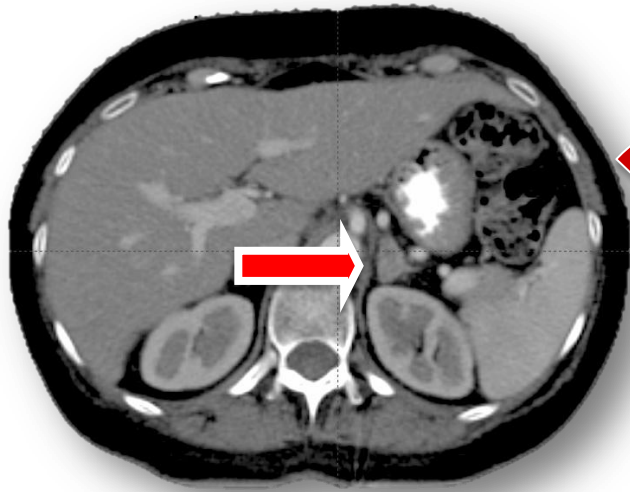
STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY (SBRT): ADRENAL GLAND METASTASES

Table 4. Summary of published trials of stereotactic body radiation therapy for adrenal metastases

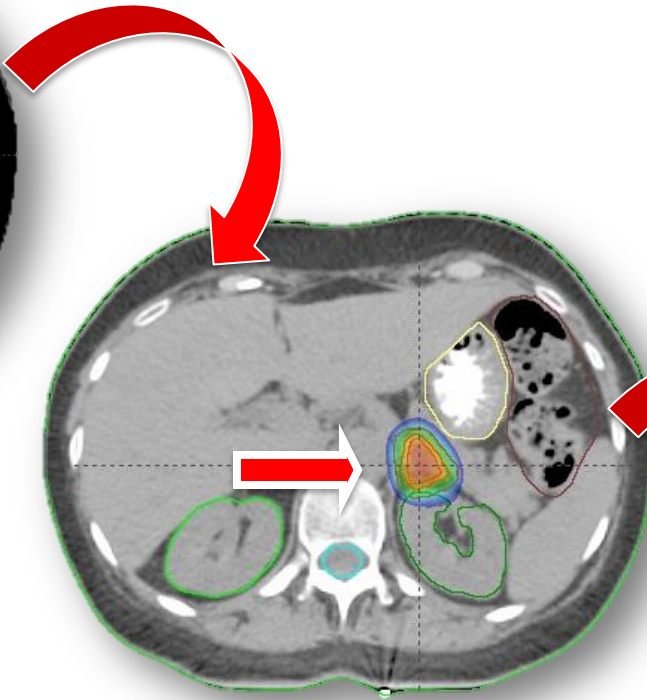
Study	<i>n</i> of patients	Median dose/ <i>n</i> of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Casamassima et al. [26]	48	36 Gy/3	16.2 (3–63)	1–2 yrs, 90%	1-yr, 39.7%; 2-yr, 14.5%	1 case of grade II adrenal insufficiency
Chawla et al. [24]	30	40 Gy/10	9.8 (3.2–28.3)	1-yr, 55%	1-yr, 44%; 2-yr, 25%	Mild grade 1 fatigue and nausea, “common”
Oshiro et al. [25]	19	45 Gy/10	11.5 (5.4–87.8)	Objective response rate, 68%	1-yr, 56%; 2-yr, 33%; 3-yr, 22%	1 grade 2 duodenal ulcer
Holy et al. [54]	18	20 Gy/5 or 40 Gy/8	21	Objective response rate, 77%	Median, 23 mos	–
Torok et al. [55]	7	16 Gy/1 or 27/3	14 (1–60)	1-yr, 63%	Median, 8 mos	–

- Few studies have been published regarding the role of SBRT in adrenal glands metastases, and several criticisms could arise regarding the lack of clear data on local control and on dose fractionation.
- Nevertheless, the good tolerability and the promising clinical results should stimulate the scientific community to further design clinical studies with the aim of optimizing local control and evaluating a potential PFS benefit.

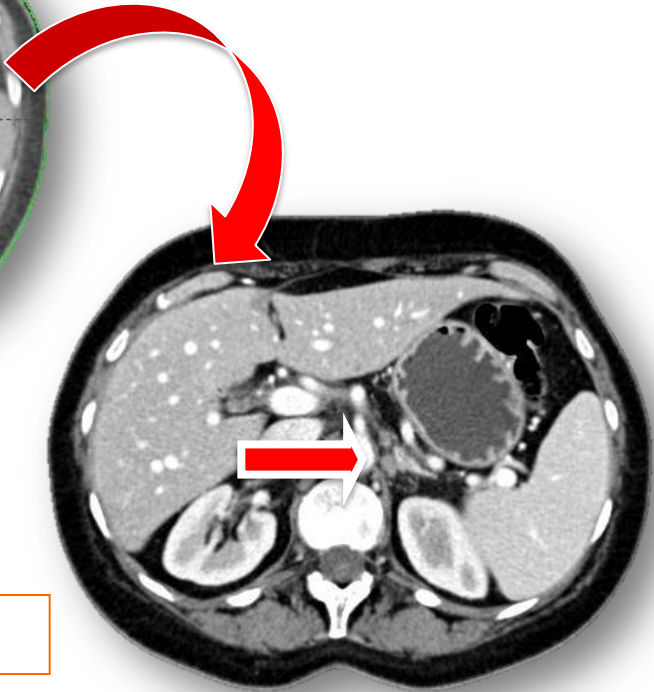
**STEREOTACTIC BODY RADIATION (ABLATIVE) THERAPY
(SBRT):
ADRENAL GLAND METASTASES**



TC pre



**SBRT:40Gy/4fr
TrueBeam FFF**



TC post

CONCLUSIONS

- Hence, based on these and other encouraging reports, *high-dose fraction* in the management of NSCLC metastases both intra- and extracranially *are increasing in interest*.

Garcia - Barros M., et al. Science, 2003

Fuks and Kolesnick, Cancer Cell 2005