

XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023

PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

Radiochirurgia encefalica: quale standard nel 2023?

Tumori secondari del sistema nervoso centrale

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Associazione Italiana
Radioterapia e Oncologia clinica

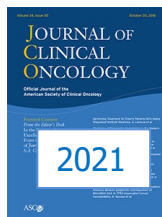
I have no disclosure

Brain metastases are the most common intracranial tumors in adults

- 10–40% of cancer patients
- The frequency of BM appears to be rising as a result of:
 - an aging population
 - the improved neuroimaging
 - the better treatment of systemic disease



Sallabanda et al. Clinical and Translational Oncology 2020



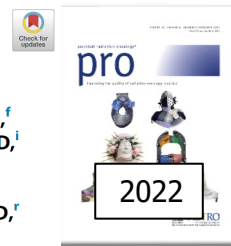
ascO special articles

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD¹; Paul D. Brown, MD²; Hans Messersmith, MPH³; Priscilla K. Brastianos, MD⁴; Stuart Burri, MD⁵; Dan Cahill, MD, PhD⁴; Ian F. Dunn, MD⁶; Laurie E. Gaspar, MD, MBA^{7,8}; Na Tosha N. Gatson, MD, PhD^{9,10}; Vinai Gondí, MD¹¹; Justin T. Jordan, MD⁴; Andrew B. Lassman, MD¹²; Julia Maues, MA¹³; Nimish Mohile, MD¹⁴; Navid Redjal, MD¹⁵; Glen Stevens, DO, PhD¹⁶; Erik Sulman, MD, PhD¹⁷; Martin van den Bent, MD¹⁸; H. James Wallace, MD¹⁹; Jeffrey S. Weinberg, MD²⁰; Gelareh Zadeh, MD, PhD²¹; and David Schiff, MD²²

Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

Vinai Gondí, MD,^{a,*} Glenn Bauman, MD,^b Lisa Bradfield, BA,^c Stuart H. Burri, MD,^d Alvin R. Cabrera, MD,^e Danielle A. Cunningham, MD,^f Bree R. Eaton, MD,^g Jona A. Hattangadi-Gluth, MD,^h Michelle M. Kim, MD,ⁱ Rupesh Kotecha, MD,^j Lianne Kraemer,^k Jing Li, MD, PhD,^l Seema Nagpal, MD,^m Chad G. Rusthoven, MD,ⁿ John H. Suh, MD,^o Wolfgang A. Tomé, PhD,^p Tony J.C. Wang, MD,^q Alexandra S. Zimmer, MD,^r Mateo Ziu, MD,^s and Paul D. Brown, MD^t

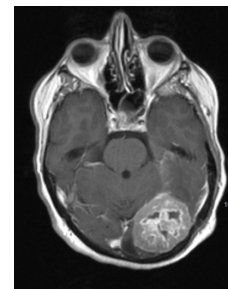
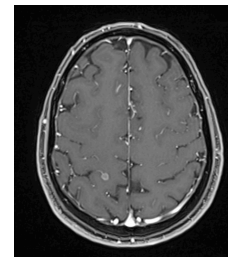
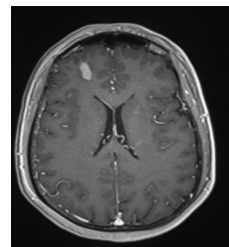


Radiation Therapy for Brain Metastases: ASCO Guideline Endorsement of ASTRO Guideline

David Schiff, MD¹; Hans Messersmith, MPH²; Priscilla K. Brastianos, MD³; Paul D. Brown, MD⁴; Stuart Burri, MD⁵; Ian F. Dunn, MD⁶; Laurie E. Gaspar, MD, MBA^{7,8}; Vinai Gondí, MD⁹; Justin T. Jordan, MD, MPH¹⁰; Julia Maues, MA¹⁰; Nimish Mohile, MD¹¹; Navid Redjal, MD¹²; Glen H.J. Stevens, DO, PhD¹³; Erik P. Sulman, MD, PhD¹⁴; Martin van den Bent, MD¹⁵; H. James Wallace, MD¹⁶; Gelareh Zadeh, MD, PhD¹⁷; and Michael A. Vogelbaum, MD, PhD¹⁸

Issues

- Limited Brain Disease
- Large Brain Metastases
- Multiple Brain Metastases



SRS alone for intact BMs (1-4)

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with an ECOG performance status of 0-2 and up to 4 intact brain metastases, SRS is recommended.	Strong	High 13-18



A Meta-Analysis Evaluating Stereotactic Radiosurgery, Whole-Brain Radiotherapy, or Both for Patients Presenting with a Limited Number of Brain Metastases

May Tsao, MD¹; Wei Xu, PhD²; and Arjun Sahgal, MD^{1,3}

Dose and Fractionation

Single dose SRS

RTOG protocol 90-05

≤ 20 mm	24 Gy	LC >90-95%
21-30 mm	18 Gy	LC 49%
31-40 mm	15 Gy	LC 45%

Single high dose SRS limited by toxicity to adjacent normal brain

Radionecrosis

most important late toxicity
up to 20%



RADIATION DOSE-VOLUME EFFECTS IN THE BRAIN

YAACOV RICHARD LAWRENCE, M.R.C.P.,* X. ALLEN LI, PH.D.,† ISSAM EL NAQA, PH.D.,‡
CAROL A. HAHN, M.D.,§ LAWRENCE B. MARKS, M.D.,¶ THOMAS E. MERCHANT, D.O. PH.D.,||
AND ADAM P. DICKER, M.D. PH.D.*



Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis

Giuseppe Minniti^{1,2*}, Enrico Clarke¹, Gaetano Lanzetta², Mattia Falchetto Osti¹, Guido Trasimeni³,
Alessandro Bozzao³, Andrea Romano³ and Riccardo Maurizi Enrici¹



IRRADIATED VOLUME AS A PREDICTOR OF BRAIN RADIONECROSIS AFTER LINEAR ACCELERATOR STEREOTACTIC RADIOSURGERY

BRIAN J. BLONIGEN, M.D.,* RYAN D. STEINMETZ, M.D.,* LINDA LEVIN, PH.D.,†
MICHAEL A. LAMBA, PH.D.,*‡ RONALD E. WARNICK, M.D.,§|| AND JOHN C. BRENNEMAN, M.D.*‡



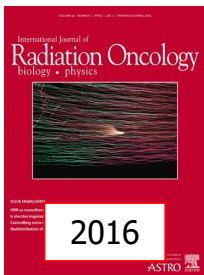
High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview

Jimm Grimm, PhD,*† Lawrence B. Marks, MD,‡ Andrew Jackson, PhD,§
Brian D. Kavanagh, MD,|| Jinyu Xue, PhD,* and Ellen Yorke, PhD§

Normal brain plus target

$$V_{12Gy} \leq 10 \text{ cc}$$

KQ4 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
<p>1. For patients with brain metastases, limiting the single-fraction V_{12Gy} to brain tissue (normal brain <i>plus</i> target volumes) to $\leq 10 \text{ cm}^3$ is conditionally recommended.</p> <p><u>Implementation remark:</u> Any brain metastasis with an associated tissue $V_{12Gy} > 10 \text{ cm}^3$ may be considered for fractionated SRS to reduce risk of radionecrosis (see KQ1).</p>	Conditional	Low 12,88



**Single-Fraction Versus Multifraction (3 × 9 Gy)
Stereotactic Radiosurgery for Large (> 2 cm)
Brain Metastases: A Comparative Analysis of
Local Control and Risk of Radiation-Induced
Brain Necrosis**



Giuseppe Minniti, MD, PhD,^{*,†} Claudia Scaringi, MD,^{*}
Sergio Paolini, MD,[†] Gaetano Lanzetta, MD,[†] Andrea Romano, MD,[‡]
Francesco Cicone, MD,[§] Mattia Osti, MD,^{*} Riccardo Maurizi Enrici, MD,^{*}
and Vincenzo Esposito, MD[†]

289 patients with brain metastases >2 cm

151pts SF-SRS 18 Gy 2-3 cm

15-16 Gy >3 cm

138pts MF-SRS 27 Gy/3 fractions

Recurrences	25 pts SF- SRS 11 pts MF-SRS	p=0.03
1 year LC rates	77% SF-SRS 91% MF-SRS	p=0.01
Brain RN	31 pts SF-SRS 11 pts MF-SRS	p=0.004
1 year RN rates	18% SF-SRS 9% MF-SRS	p=0.01

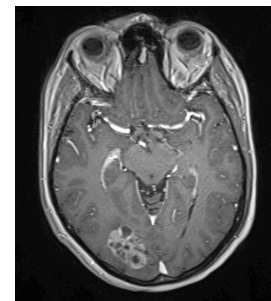
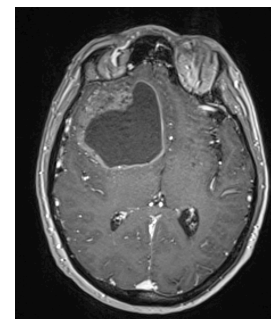
MF-SRS effective treatment for large BMs associated with **better LC** and reduced risk of **RN** compared with SF-SRS

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
<p>3. For patients with intact brain metastases measuring <u><2 cm</u> in diameter, single-fraction SRS with a dose of <u>2000-2400 cGy</u> is recommended.</p> <p><u>Implementation remark:</u> If multifraction SRS were chosen (eg, V12 Gy >10 cm³ [see KQ4]), options include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions.</p>	Strong	Moderate 5,13,16,19,22
<p>4. For patients with intact brain metastases measuring <u>≥2 to <3 cm</u> in diameter, single-fraction SRS using 1800 cGy or multifraction SRS (eg, <u>2700 cGy in 3 fractions</u> or 3000 cGy in 5 fractions) is conditionally recommended (see KQ4).</p>	Conditional	Low 22-24
<p>5. For patients with intact brain metastases measuring <u>≥3 to 4 cm</u> in diameter, multifraction SRS (eg, <u>2700 cGy in 3 fractions</u> or <u>3000 cGy in 5 fractions</u>) is conditionally recommended.</p> <p><u>Implementation remarks:</u></p> <ul style="list-style-type: none"> • If single-fraction SRS were chosen, doses up to 1500 cGy may be used (see KQ4). • Multidisciplinary discussion with neurosurgery to consider surgical resection is suggested for all tumors causing mass effect, irrespective of tumor size. 	Conditional	Low 23,24
<p>6. For patients with intact brain metastases measuring <u>>4 cm</u> in diameter, surgery is conditionally recommended, and if not feasible, <u>multifraction SRS</u> is preferred over single-fraction SRS.</p> <p><u>Implementation remark:</u> Given limited evidence, SRS for tumor size >6 cm is discouraged.</p>	Conditional	Low 19,22-24

Surgery & SRS-HSRS

Surgical resection evaluation:

- **limited number** (1 to 4) of newly diagnosed brain metastases
- in case of lesions of **≥ 2.1 cm** in diameter (symptomatic or not)
- lesions with **necrotic or cystic** appearance
- **edema/mass effect**
- lesions located in the **posterior fossa** with associated hydrocephalus
- lesions located in symptomatic **eloquent areas**



Surgery & SRS-HSRS

Surgery alone

Local recurrence 46-59%

Surgery + WBRT

Local recurrence 10-28%

No OS benefit

WBRT:

Decline of **neurocognitive function** and quality of life

Patchell et al, JAMA 1998

Kocher et al, JCO 2011



Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Anita Mahajan MD^a, Salmaan Ahmed MD^b, Mary Frances McAleer MD^c, Jeffrey S Weinberg MD^d, Ling Li MD^c, Paul Brown MD^c, Stephen Settle MD^c, Sujit S Prabhu MD^d, Frederick F Lang MD^d, Nicholas Levine MD^d, Susan McGovern MD^c, Erik Sulman MD^c, Ian E McCutcheon MD^d, Syed Azeem MD^d, Daniel Cahill MD^d, Claudio Tatsui MD^d, Amy B Heimberger MD^d, Sherise Ferguson MD^d, Amol Ghia MD^c, Franco Demonte MD^d...Dr Ganesh Rao MD^d  

132 patients

1-3 BMs

KPS>70%

Maximum diameter \leq 4cm

SRS

16 Gy (range 12–18) to the 50% isodose line

12-month freedom from LR

68 observation group

43%

64 SRS group

72%

p=0.015

Postoperative SRS/HSRS:

Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases

Giuseppe Minniti¹, Vincenzo Esposito, Enrico Clarke, Claudia Scaringi, Gaetano Lanzetta, Maurizio Salvati, Antonino Raco, Alessandro Bozzao, Riccardo Maurizi Enrici



2013

101 patients

1- 2-year LC	93% - 84%
1- 2-year BDF	50% - 66%
RN	9%

SRS s
Radiat C

Surgery Followed by Hypofractionated Radiosurgery on the Tumor Bed in Oligometastatic Patients With Large Brain Metastases. Results of a Phase 2 Study

Pierina Navarra¹, Federico Pessina², Elena Clerici³, Davide Franceschini³, Lorenzo Gabriel Gay⁴, Fiorenza De Rose³, Ilaria Renna³, Giuseppe D'Agostino³, Ciro Franzese³, Tiziana Comito³, Stefano Tomatis³, Marco Conti Nibali⁴, Antonella Leonetti⁴, Guglielmo Puglisi⁴, Lorenzo Bello⁵, Marta Scorsetti⁶



2019

101 patients

1- 2-year LC	99% - 86%
1- 2-year BDF	31% - 49%
G3 RN	6%

Postoperative SRS/HSRS: Meningeal Disease

The shift from postoperative WBRT to tumor cavity focal therapy has led to the observation of a unique form of recurrence:

nodular meningeal disease

Surgical perturbation of the tumor

risk of **tumor spillage** via the cerebrospinal fluid
development of nodular tumor recurrence

Risk of nodular meningeal disease at 1-year

28%
poor survival outcomes
up to three fourths having a neurologic death

Mahajan A, et al. Lancet Oncol. 2017
Prabhu RS, et al. Neuro-Oncol. 2019
Cagney DN, et al. JAMA Oncol. 2019

Preoperative SRS/HSRS

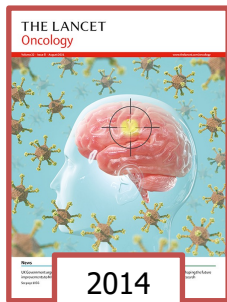
Several potential advantages:

- a **better target delineation** to an intact lesion
- the **reduction of normal brain irradiated** considering the useless of additional margins
- the potential **prevention** of any cells spilled during resection
- a **greater oxygenation** ratio of the intact region
- a sterilization effect
- the **resection** of the majority of **irradiated tissues**

	Pts	Diam	Volume	doses	6m LC	12mLC	24mLC	RN	LMD	BDF%	mBDF
Asher R+P 2013	47 pts	3.04 cm (1.34-5.21 cm)	8.49 cc (0.89-46.7 cc)	14 Gy (11.6-18 Gy) 80%	98%	86%	72%	0	no	38	8 m
Patel K., J Neurooncol 2016 R	66*	NA	8.3cc	14.5Gy	94.2%	84.2%	77.2%	1.5% 1y 4.9% 2 y	3.2%	NA	NA
Prabhu , JNS 2018 R-P	117 24 p 93 r	NA	8.3 cc (4.6– 13.3cc)	15 Gy (14– 17 Gy)	NA	80%	75%	4.8% G2-G3	5.1% At mtime 11.6 m	60% (at 2 years)	NA
Patel K., J Neurooncol 2017 R	66	NA	8.3cc	14.8 (12.0– 19.0)	NA	NA	75.5%	5.6%	3.5%	53.2%	NA
Patel A., WN 2018 R	12	3.66(2.19- 4.85)	14.69 cc (3.38-34.85)	16 (12-21)	82%	49%	NA	0	17% (2pts) at mtime 11.3m	67% (8pts)	7.2m

Study Title	Status	Conditions	Interventions	Sponsor
Trial of Preoperative Radiosurgery Versus Postoperative Stereotactic Radiotherapy for Resectable Brain Metastases	Recruiting	<ul style="list-style-type: none"> Brain Metastases, Adult 	<ul style="list-style-type: none"> Radiation: preoperative radiosurgery Radiation: postoperative hypofractionated stereotactic radiotherapy 	Susanne Rogers
A Phase II Study of Pre-Op SRS Followed by Surgical Resection for Brain Metastases	Recruiting	<ul style="list-style-type: none"> Brain Metastases, Adult 	<ul style="list-style-type: none"> Other: Pre-operative Stereotactic Radiosurgery 	Allegheny Singer Research Institute (also known as Allegheny Health Network Research Institute)
Preoperative vs Postoperative Hypofractionated Radiosurgery for Patients With Large Brain Metastases	Recruiting	<ul style="list-style-type: none"> Brain Metastases, Adult 	<ul style="list-style-type: none"> Radiation: Hypofractionated Radiosurgery (HSRS) Procedure: Brain metastases surgical resection 	Istituto Clinico Humanitas

SRS alone for intact multiple BMs (>4)



Stereotactic radiosurgery for patients with multiple brain metastases (JLJK0901): a multi-institutional prospective observational study



Masaaki Yamamoto*, Toru Serizawa*, Takashi Shutō, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jakura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya

Aim: whether SRS without WBRT for patients with 5-10 BMs is non-inferior to that for patients with 2-4 BMs in terms of OS

Prospective observational study **1194** patients

BM <10 mL and <3 cm - **total cumulative volume ≤15 mL**

BM <4 mL 22 Gy

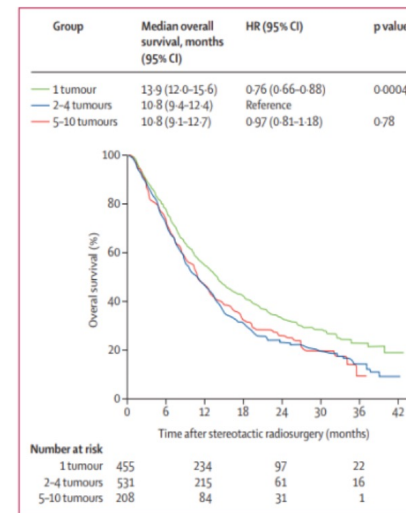
BM 4–10 mL 20 Gy

mOS

13.9 months	455 pts 1 BM
10.8 months	531 pts 2-4 BMs
10.8 months	208 pts 5-10 BMs

TRT

50 (9%)	pts 2-4 BMs
18 (9%)	pts 5-10 BMs



Conclusion

SRS without WBRT in pts with 5-10 BMs is **non-inferior** to pts with 2-4 BMs

Considering the **minimal invasiveness** of SRS and the **fewer side-effects** than WBRT, it might be a suitable alternative for patients with **up to 10 BMs**



Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience

Ryan T. Hughes, MD,* Adrianna H. Masters, MD, PhD,*
Emory R. McTyre, MD, MS,* Michael K. Farris, MD,*
Caroline Chung, MD, MSc,[†] Brandi R. Page, MD,[‡]
Lawrence R. Kleinberg, MD,[‡] Jaroslaw Hepel, MD,[§]
Joseph N. Contessa, MD, PhD,^{||} Veronica Chiang, MD,[¶]
Jimmy Ruiz, MD,[#] Kounosuke Watabe, PhD,** Jing Su, PhD,^{††}
John B. Fiveash, MD,^{‡‡} Steve Braunstein, MD, PhD,^{§§}
Samuel Chao, MD,^{||||} Albert Attia, MD,^{¶¶}
Diandra N. Ayala-Peacock, MD,^{¶¶} and Michael D. Chan, MD*

mOS

14.6 months

989 pts 1 BM

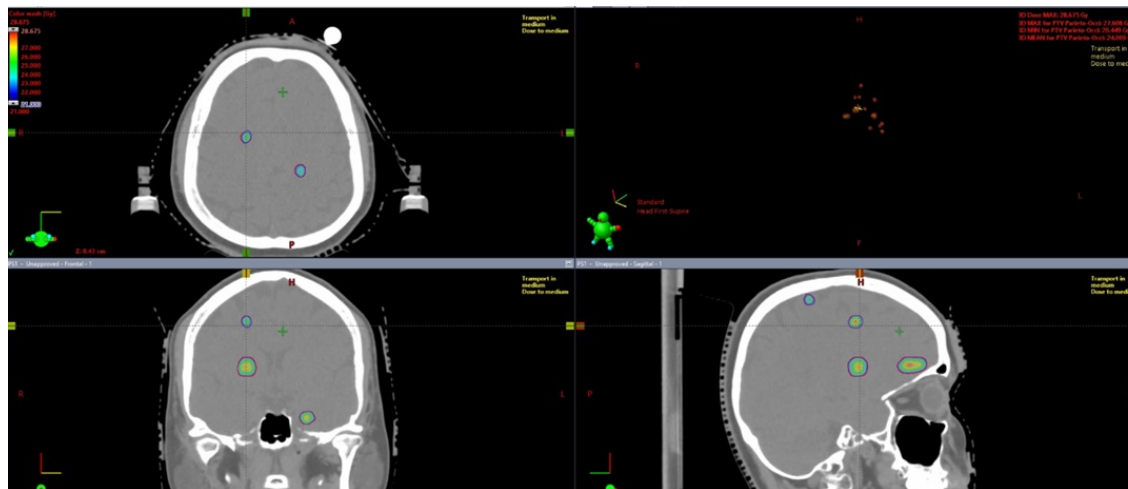
9.5 months

882 pts 2-4 BMs

7.5 months

212 pts 5-15 BMs

5-10 BMs 190 pts
11-15 BMs 22 pts



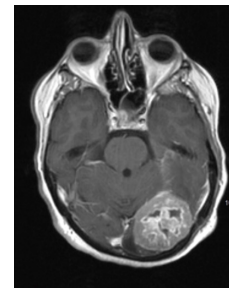
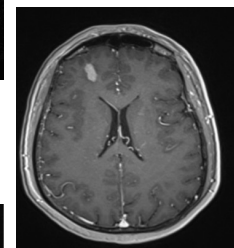
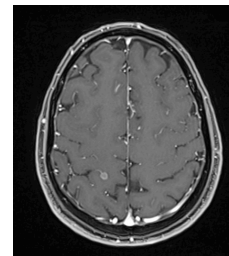
KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
2. For patients with an ECOG performance status of 0-2 and 5-10 intact brain metastases, SRS is conditionally recommended.	Conditional	Low 19-21

Study Title	Status	Conditions	Interventions
Radiosurgery With or Without Whole Brain Radiation for Multiple Metastases	Recruiting	<ul style="list-style-type: none"> Brain Metastases 	<ul style="list-style-type: none"> Radiation: Stereotactic Radiosurgery (SRS) Radiation: Whole brain radiation (WBRT)
Neurocognitive Decline in Patients With Brain Metastases	Recruiting	<ul style="list-style-type: none"> Brain Metastases 	<ul style="list-style-type: none"> Radiation: Stereotactic Radiosurgery
The CyberChallenge Trial How Much is Too Much - What is the Role of Cyberknife Radiosurgery in Patients With Multiple Brain Metastases?	Recruiting	<ul style="list-style-type: none"> Brain Metastases Nsclc 	<ul style="list-style-type: none"> Radiation: SRS Radiation: Whole Brain Radiotherapy
WHOLE Brain Irradiation or Stereotactic Radiosurgery for Five or More Brain Metastases (WHOBISTAR)	Recruiting	<ul style="list-style-type: none"> Neurocognitive Deficit Quality of Life Activities of Daily Living 	<ul style="list-style-type: none"> Radiation: Stereotactic RadioTherapy Radiation: Whole Brain Irradiation

Take home messages

- Limited Brain Disease:
 - SRS, strong recommendation
- Large Brain Metastases
 - MF-SRS
 - SRS on surgical cavity
- Multiple Brain Metastases
 - SRS, conditional recommendation

$$V_{12\text{Gy}} \leq 10 \text{ cc}$$



AIRO2023

Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti



*thank
you*

