MALIGNANT CNS TUMORS: STEREOTAXY & BEYOND

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Stereotactic Radiosurgery(SRS)

Delivered with

- Gamma Knife

- Modified LINAC radiosurgery systems (including CyberKnife & Image-guided radiotherapy systems)

- TomoTherapy

- Proton beam systems

Common Indications for Radiosurgery or Hypofractionated Stereotactic Radiotherapy

Indication	Experience	Value
Functional a. Trigeminal neuralgia b. Unilateral tremor	a. Extensive b. Moderate	1. Less numbness than rhizotomy 2. In poor candidates for deep brain stimulation
Vascular a. AVM b. Cavernous	a. Extensive b. Moderate	a. High b. Controversial
Benign tumors: schwannoma, pituitary adenoma meningioma, etc.	Extensive	High tumor control, acceptable morbidity for selected small tumors
Brain metastases	Extensive	Control rates ≥ surgery for small mets
Primary malignant brain tumors	Extensive for GBM. Limited with other uses	Initial SRS appears ineffective for GBM. Helpful for recurrent tumors, possibly initial pilocytic, neurocytoma
Spinal metastases	Moderate	High for recurrent tumors. No phase 3 comparison with conventional XRT for initial treatment

Perez & Brady's Principles and Practice of Radiation Oncology, 7th edition

Brain metastases

- Most common intracranial tumors in adults
- Estimated 10–40% of cancer patients develop metastases during course of illness
- Most common in patients with lung, breast, melanoma, renal cell, & gastrointestinal carcinoma
- Historically, whole brain radiation therapy (WBRT): Standard of care

Brain metastases

- Improved extracranial control and prognosis due to development of better systemic therapies & surgical techniques

- Optimizing intracranial control while minimizing late neurotoxicity important

Estimating Prognosis of Patients with Brain Metastasis

Recursive partitioning analysis (RPA)

- Radiation Therapy Oncology Group's (RTOG's) RPA first published in 1997
- Stratifies patients with brain metastases into three classes
- Class I: Karnofsky performance status (KPS) ≥ 70, < 65 years of age with controlled primary & no extracranial metastases

  Class III: KPS < 70

  Class II: all others

(Gaspar et al., 1997)

Graded prognostic assessment (GPA)

- First published in 2008 based on patients from five randomized RTOG trials
- Four prognostic factors—age, KPS, extracranial metastases & number of brain metastases
- 2010: Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)
- Breast GPA: molecular subtypes included
- molGPA: GPA incorporates molecular factors (EGFR and ALK gene alterations in NSCLC & BRAF status in melanoma)

Sperduto, Paul W et al. "Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient." *Journal of clinical oncology* (2020): 3773-3784

Breast GPA

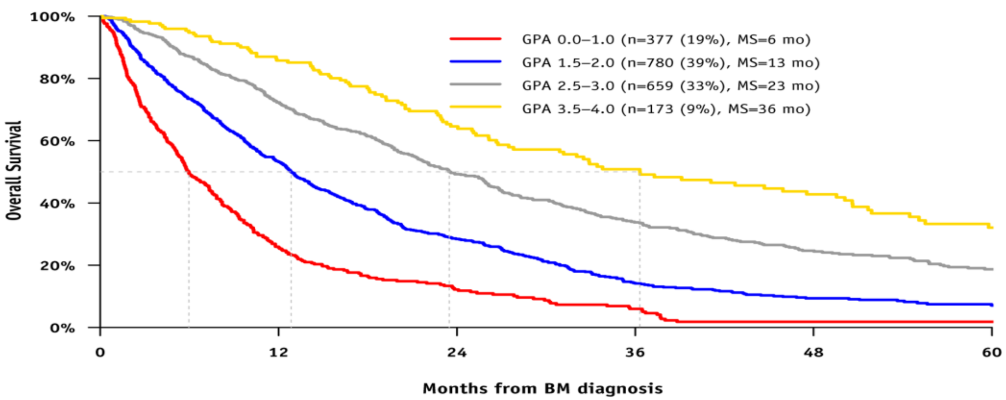
Table 3 Definition/Worksheet for the Updated Graded Prognostic Assessment for Breast Cancer Patients with Brain Metastases (Breast GPA) and Survival by GPA

Factor	0	0.5	1.0	1.5	Patient Score
KPS	≤ 60	70-80	90-100	NA	
Subtype	Basal	Luminal A	NA	Her 2, Luminal B	
Age	≥ 60	< 60	NA	NA	
Number BM	> 1	1	NA	NA	
ECM	Present	Absent			
					Sum Total =

Survival by GPA

GPA	N (%)	Median OS	IQR
0.0 − 1.0	377 (19%)	6.0	2.5-12.3
1.5 − 2.0	780 (39%)	12.9	5.6-27.0
2.5 − 3.0	659 (33%)	23.5	11.1-47.0
3.5 − 4.0	173 (9%)	36.3	18.5-78.1

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; HER2 = human epidermal receptor2; IQR = interquartile range; KPS = Karnofsky Performance Status; OS = overall survival.
Basal (HR/HER2-negative); Luminal A (HR-positive/HER2-negative); Luminal B (HR/HER2-positive); HER2 (HR-negative/HER2-positive).



Number at risk

	0	12	24	36	48	60
GPA 0.0–1.0	377	85	32	13	3	2
GPA 1.5–2.0	780	377	165	72	39	16
GPA 2.5–3.0	659	453	264	149	92	54
GPA 3.5–4.0	173	141	88	60	45	26

Kaplan Meier Curves for Survival by Breast GPA

GPA of 0: Worst prognosis
GPA of 4.0: Best prognosis

Sperduto, Paul W et al. "Beyond an Updated Graded Prognostic Assessment (Breast GPA): A Prognostic Index and Trends in Treatment and Survival in Breast Cancer Brain Metastases From 1985 to Today." International journal of radiation oncology, biology, physics vol. 107,2 (2020): 334-343

SRS: What is the maximum tolerated dose?

SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05

EDWARD SHAW, M.D.,* CHARLES SCOTT, PH.D.,† LUIS SOUHAMI, M.D.,‡ ROBERT DINAPOLI, M.D.,§ ROBERT KLINE, PH.D.,|| JAY LOEFFLER, M.D.,¶ AND NANCY FARNAN, B.S.†

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 2, pp. 291–298, 2000

Purpose: To determine the maximum tolerated dose of single fraction radiosurgery in patients with recurrent previously irradiated primary brain tumors & brain metastases.

RTOG PROTOCOL 90-05

- Between 1990–1994
- 156 patients : 36% recurrent primary brain tumors (median prior dose 60 Gy) & 64% recurrent brain metastases (median prior dose 30 Gy)
- Initial radiosurgical doses :18 Gy for tumors < 20 mm, 15 Gy for tumors 21–30 mm, &12 Gy for 31–40 mm in maximum diameter

RTOG PROTOCOL 90-05

- Doses escalated in 3 Gy, & incidence of irreversible grade 3-5 Radiation Therapy Oncology Group (RTOG) neurotoxicity assessed.
- Maximum tolerated doses: 24 Gy for tumors < 20 mm,
  18 Gy for tumors 21–30 mm
  15 Gy for 31–40 mm
- For tumors < 20 mm, investigators' reluctance to escalate to 27 Gy, rather than excessive toxicity, determined the maximum tolerated dose

Critical Structures & Tolerance for Intracranial SRS

Summary of Relevant Dose Tolerances Of Primary Intracranial Structures within the Context of Single-Fraction SRS

OAR	Dose Tolerance	Clinical Endpoint	Note
Brain	V_{12} <5–10 cm^3 (10% risk) V_{14} <5 cm^3 (<1 % risk)	Radionecrosis	Tolerance and clinical sensitivity dependent on location and eloquence
Brainstem	D_{max} <12.5 Gy (<5% risk) $D_{0.5cm3}$ <10 Gy	Radionecrosis Neuropathy	For brainstem metastasis, 15 Gy to lesions <2 cm in volume is practiced
Optic Pathway	D_{max} <10 Gy (<1% risk) $D_{0.2cm3}$ <8 Gy	Radiation-induced optic neuropathy (RION)	Refers to optic nerves and chiasm
Cochlea	D_{max} <9 Gy D_{mean} or $D_{modiolus}$ <4 Gy	Sensorinueral hearing loss	Cochlear nucleus may also be important but further data required

Intracranial Stereotactic Radiosurgery, Jason P. Sheehan, L. Dade Lunsford, 3rd edition, Page 72

What are the indications for SRS alone for patients with intact brain metastases?

Three randomized controlled trials (RCTs) compared SRS alone to SRS plus WBRT

- JROSG 99-1 (Aoyama et al. 2006)
- MDACC (Chang et al. 2009)
- NCCTG (Brown et al. 2016)

Two RCTs compared local therapy alone (SRS or surgery) to local therapy plus WBRT.

- EORTC 22952-26001 (Kocher et al. 2011)
- Hong et al. 2019

Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

JAMA. 2006;295:2483-2491

- Randomized multi-institution trial by Japanese Radiation Oncology Study Group (JROSG 99-1)
- 132 patients with 1–4 brain metastases (dia. < 3 cm) & KPS ≥70
- SRS (18–25 Gy/1 fraction) vs. WBRT(30 Gy/10 fractions) followed by SRS

JROSG 99-1 (Aoyama et al. 2006)

- Addition of WBRT reduced rate of new metastases (64% vs. 42%), need for salvage brain treatment, & improved 1-year recurrence rate (47%vs. 76%).
- No difference in OS (~8 months), neurologic or KPS preservation, or Mini-Mental State Examination (MMSE) score

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

Lancet Oncol 2009; 10: 1037–44

- Randomized trial by MD Anderson Cancer Center
- 58 patients with 1–3 brain metastases and KPS ≥70
- SRS (15–24 Gy/1 fraction) vs. SRS + WBRT
- Formal neurocognitive testing

MDACC (Chang et al. 2009)

- Trial stopped early: Decline in memory and learning at 4 months with WBRT by Hopkins Verbal Learning Test (52% vs. 24%).

- WBRT associated with improved LC (100% vs. 67%) & distant brain control (73% vs.45%) at 1 year

- Significantly longer OS with SRS alone (15 vs. 6 months)- Patients in this arm received more salvage therapy including repeat SRS (27 vs. 3 retreatments)

Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases

A Randomized Clinical Trial

JAMA. 2016;316(4):401-409

Paul D. Brown, MD[1,2]; Kurt Jaeckle, MD[3]; Karla V. Ballman, PhD[4]; et al

- Prospective phase III randomized trial by North Central Cancer Treatment Group (NCCTG)
- SRS alone or SRS+WBRT for 1–3 brain metastases
- Primary endpoint: Neurocognitive deterioration at 3 months
- 213 participants showed less cognitive deterioration at 3 months after SRS alone (63.5%) compared to SRS and WBRT (91.7%) $p < 0.001$

NCCTG (Brown et al. 2016)

- Time to intracranial failure: Significantly shorter for SRS alone (HR 3.6; $p < 0.001$)
- No significant difference in OS at 10.4 months for SRS alone and 7.4 months for SRS plus WBRT ($p = 0.92$)

Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

J Clin Oncol. 2011 Jan 10; 29(2): 134–141

- Randomized phase III trial of the European Organisation for Research and Treatment of Cancer (EORTC)
- 359 patients with 1-3 brain metastases & WHO performance status (PS) of 0 to 2 treated with complete surgery or radiosurgery
- Randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS)
- Primary end point: Time to WHO PS deterioration to >2

EORTC 22952-26001 (Kocher et al. 2011)

- Median time to WHO PS >2 : 10.0 months (95% CI, 8.1 to 11.7 months) after OBS & 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT (P=.71)

- Overall survival: Similar in WBRT & OBS arms (median, 10.9 v 10.7 months, respectively; P= .89)

- WBRT reduced 2-year relapse rate both at initial sites (surgery: 59% to 27%, P < .001; radiosurgery: 31% to 19%, P = .040) & at new sites (surgery: 42%to 23%, P = .008; radiosurgery: 48% to 33%, P = .023).

EORTC 22952-26001 (Kocher et al. 2011)

- Intracranial progression caused death in 78 (44%) of 179 patients in OBS arm & in 50 (28%) of 180 patients in WBRT arm

- After radiosurgery or surgery of a limited number of brain metastases, adjuvant WBRT reduces intracranial relapses & neurologic deaths but fails to improve the duration of functional independence & OS

Adjuvant Whole-Brain Radiation Therapy Compared With Observation After Local Treatment of Melanoma Brain Metastases: A Multicenter, Randomized Phase III Trial

Angela M. Hong, MBBS, PhD[1,2]; Gerald B. Fogarty, MBBS, PhD[1,2]; Kari Dolven-Jacobsen, PhD[3]; Bryan H. Burmeister, MBBS[4,5]; Serigne N. Lo, PhD[1,6]; Lauren E. Haydu, PhD, MPH[7]; Janette L. Vardy, MD, PhD[1,8]; Anna K. Nowak, PhD[9]; Haryana M. Dhillon, PhD[1]; Tasnia Ahmed, MS[1]; Brindha Shivalingam, MBBS[1,2,10]; Georgina V. Long, MBBS, PhD[1,11]; Alexander M. Menzies, MBBS, PhD[1,11]; George Hruby, MBChB[1,2,11]; Katharine J. Drummond, MD[12,13]; Catherine Mandel, MBBS[14]; Mark R. Middleton, PhD[15]; Claudius H. Reisse, MD[3]; Elizabeth J. Paton, MSc[1]; Victoria Steel, BSc[1]; Narelle C. Williams, MPH[1]; Richard A. Scolyer, MBBS, MD[1,10]; Rachael L. Morton, MSc, PhD[1]; and John F. Thompson, MBBS, MD[1,10]

J Clin Oncol 37:3132-3141

- Randomized phase III trial
- 215 patients with 1-3 melanoma brain metastases locally treated by either surgery and/or SRS
- Randomly assigned to adjuvant WBRT or observation (OBS)
- Primary end point: Distant intracranial failure within 12 months
- Secondary end points: Time to intracranial failure, survival, & time to deterioration in PS

Hong et al.(2019)

- Forty-two percent of patients in WBRT group & 50.5% in observation developed distant intracranial failure within 12 months (odds ratio, 0.71;95% CI, 0.41 to 1.23; P = .22)

- At 12 months, 41.5% of patients in WBRT group & 51.4% of patients in observation group had died (P = .28), with no difference in rate of neurologic death.

- Median time to deterioration in PS: 3.8 months after WBRT & 4.4 months with observation (P = .32)

- After local treatment of 1-3 melanoma brain metastases, adjuvant WBRT does not provide clinical benefit in terms of distant intracranial control, survival, or preservation of PS

Clinical Practice Guideline

Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

Vinai Gondi, 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[f]

Practical Radiation Oncology® (2022) **12**, 265–282

"Strong recommendations are made for SRS for patients with limited brain metastases and Eastern Cooperative Oncology Group performance status 0 to 2"

Table 3 Indications for SRS alone for intact brain metastases

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]
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]
3. For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000-2400 cGy is recommended. Implementation remark: If multifraction SRS were chosen (eg, V12 Gy >10 cm^3 [see KQ4]), options include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions.	Strong	Moderate [5,13,16,19,22]
4. For patients with intact brain metastases measuring ≥2 to <3 cm in diameter, single-fraction SRS using 1800 cGy or multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended (see KQ4).	Conditional	Low [22-24]
5. For patients with intact brain metastases measuring ≥3 to 4 cm in diameter, multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended. Implementation remarks: • 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]
6. For patients with intact brain metastases measuring >4 cm in diameter, surgery is conditionally recommended, and if not feasible, multifraction SRS is preferred over single-fraction SRS. Implementation remark: Given limited evidence, SRS for tumor size >6 cm is discouraged.	Conditional	Low [19,22-24]
7. For patients with *symptomatic* brain metastases who are candidates for local therapy and CNS-active systemic therapy, upfront local therapy is recommended.	Strong	Low [25,26]
8. For patients with *asymptomatic* brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred. Implementation remark: The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert opinion

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; KQ = key question; SRS = stereotactic radiosurgery. Local therapy is defined as brain metastasis-directed radiation therapy and/or surgery.

Indications for observation, preoperative SRS, or postoperative SRS or WBRT in patients with resected brain metastases

Table 4 Indications for observation, postoperative SRS, WBRT, or preoperative SRS

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with resected brain metastases, radiation therapy (SRS or WBRT) is recommended to improve intracranial disease control.	Strong	High 13,50,51
2. For patients with resected brain metastases and limited additional brain metastases, SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QoL.	Strong	Moderate 52
3. For patients whose brain metastasis is planned for resection, preoperative SRS is conditionally recommended as a potential alternative to postoperative SRS.	Conditional	Low 53,54

Abbreviations: KQ = key question; QoL = quality of life; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

V. Gondi et al

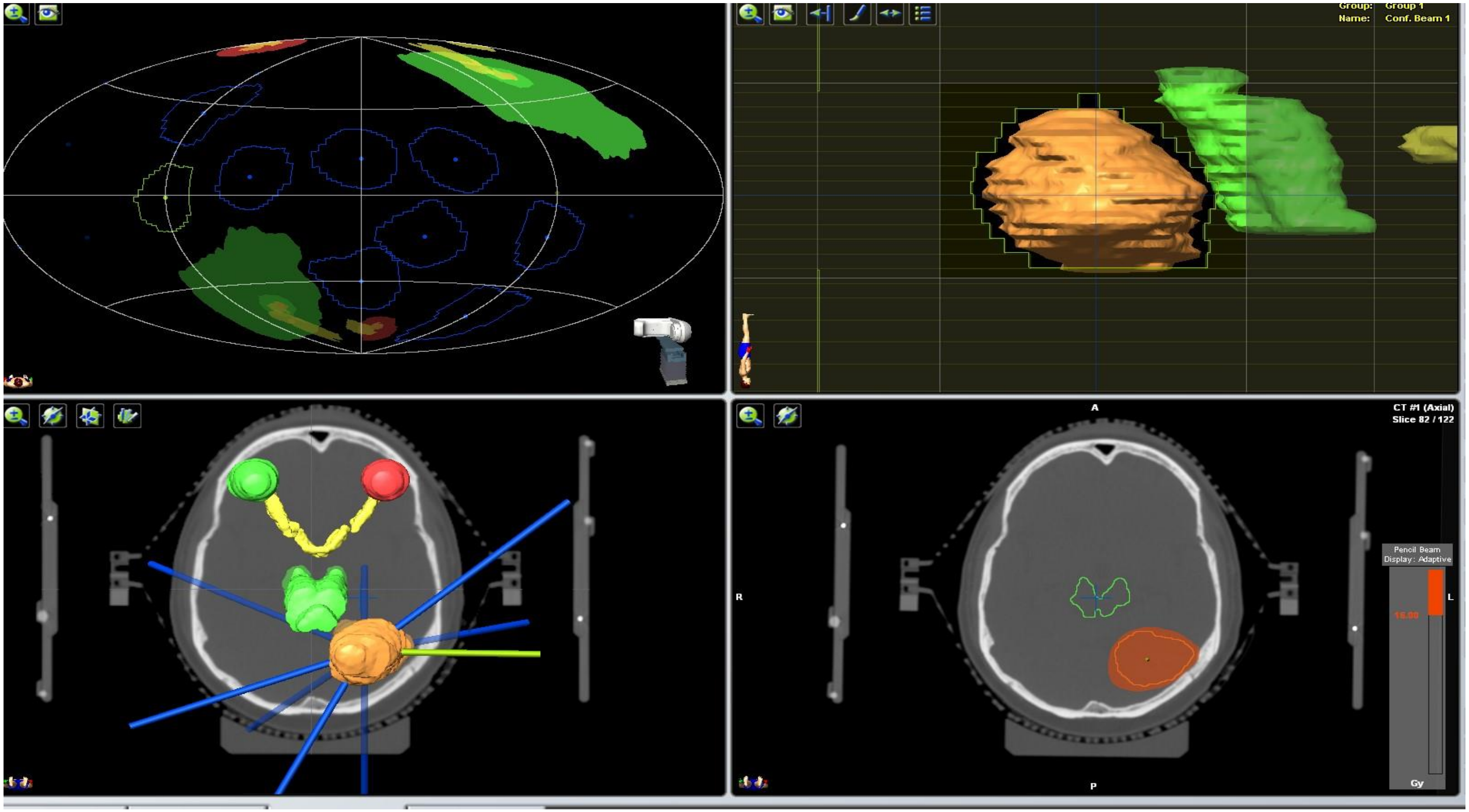
Practical Radiation Oncology® (2022) **12**, 265–282

Table 5 Recommended postoperative cavity single-fraction SRS dosing guidance[52]

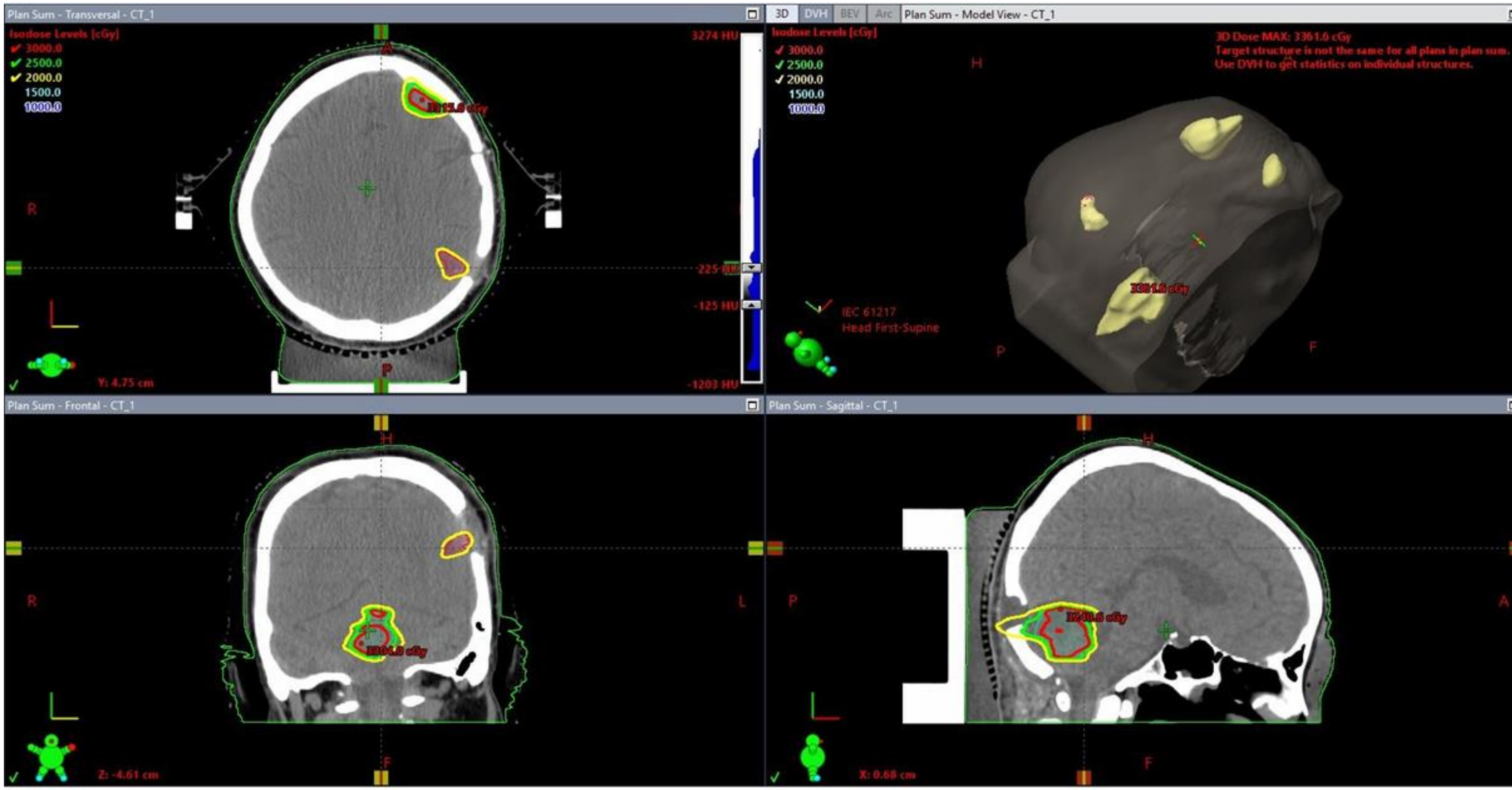
Cavity volume (cm^3)*	Single-fraction SRS dose (cGy)
<4.2 cm^3	2000 cGy
≥4.2 to <8.0 cm^3	1800 cGy
≥8.0 to <14.4 cm^3	1700 cGy
≥14.4 to <20.0 cm^3	1500 cGy
≥20.0 to <30.0 cm^3	1400 cGy
≥30.0 cm^3 to <5.0 cm max	1200 cGy

Abbreviation: SRS = stereotactic radiosurgery.

* Given the irregular shape of surgical cavities, the total prescribed dose should be based on the surgical cavity volume with a maximum cross-sectional diameter of <5.0 cm.



Case 01: A 37-year-old woman treated for carcinoma ovary was evaluated for headache and vomiting. MRI Brain revealed a lesion in the left cerebellar hemisphere suggestive of solitary brain metastasis. She was treated with SRS alone. A dose of 16 Gy was delivered in single fraction by Conformal Radiotherapy using 9 non-coplanar beams.



Case 02: A 51-year-old woman with HER 2 positive breast cancer, post-surgery, chemotherapy and anti-HER-2 therapy was evaluated for vertigo. MRI brain revealed 4 lesions (involving posterior fossa, bilateral frontal regions and left parietal lobe) suggestive of metastasis. She underwent surgical excision of all 4 metastatic brain lesions. Histopathology review was consistent with metastasis from invasive carcinoma breast, positive for Estrogen receptor (Allred sore 7), Progesterone receptor (Allred sore 5) and Her-2 Neu protein (score 3+). Postoperatively she was treated with Linac based Volumetric Modulated Arc Therapy(VMAT) for her brain metastasis. The cerebellar and right frontal lesions were treated with 25 Gy in 5 fractions. Left frontal and left parietal lesions were treated with a dose of 20 Gy/single fraction.

Primary malignant brain tumors

- First-line treatment of Glioblastoma: Maximum resection followed by adjuvant chemoradiation with temozolomide as defined through the Stupp trial (Stupp et al. 2005)

- Dose: 60 Gy in 30 fractions

- For elderly patients multiple RCTs (Perry et al. 2017; Roa 2004, 2015) established similar efficacy with shorter hypofractionated schedules (e.g., 40 Gy in 15 fractions or 25 Gy in 5 fractions)

SRS as part of upfront treatment of High-Grade Gliomas

RANDOMIZED COMPARISON OF STEREOTACTIC RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE TO CONVENTIONAL RADIOTHERAPY WITH CARMUSTINE FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: REPORT OF RADIATION THERAPY ONCOLOGY GROUP 93-05 PROTOCOL

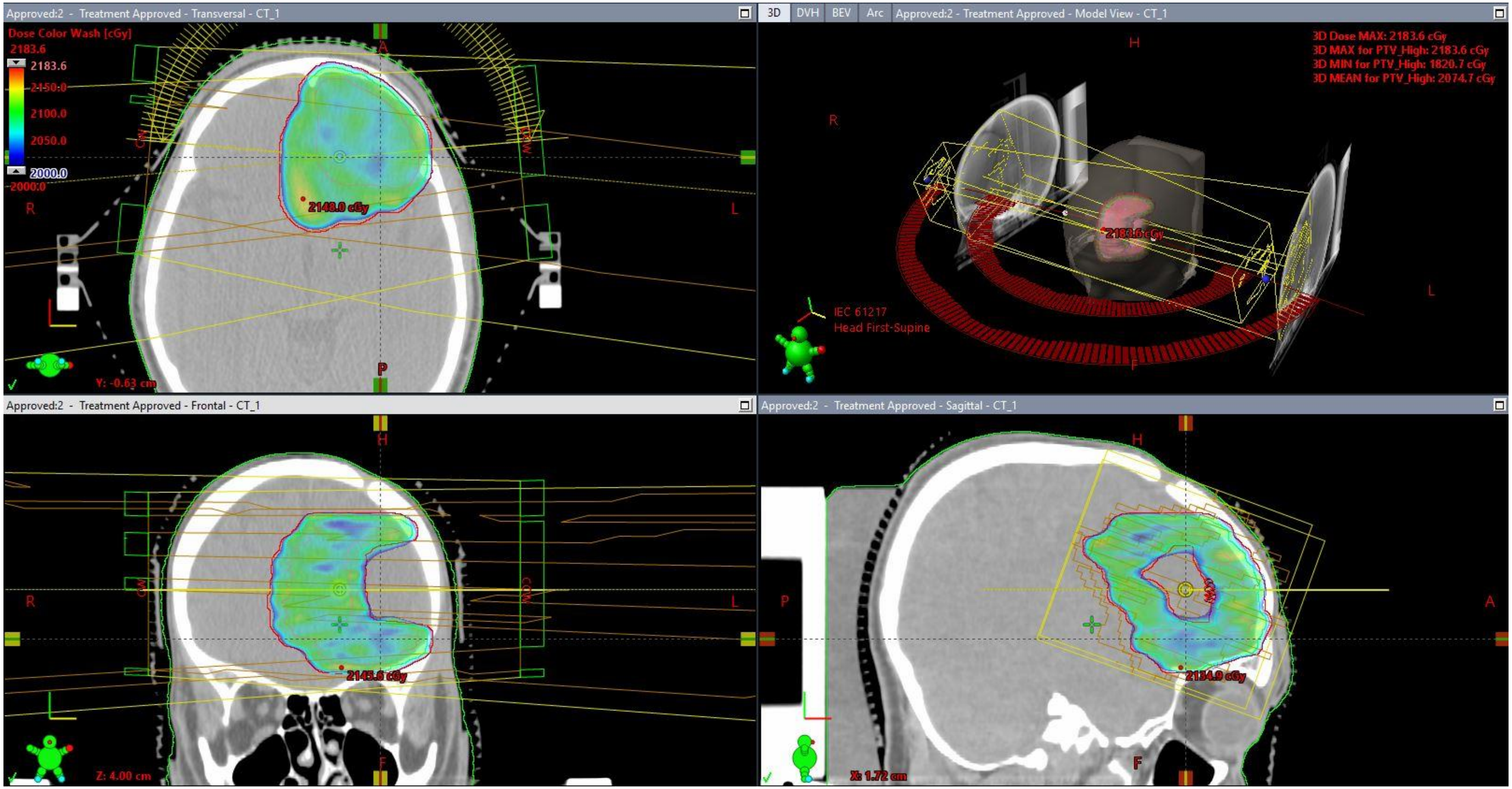
LUIS SOUHAMI, M.D.,[*] WENDY SEIFERHELD, M.S.,[†] DAVID BRACHMAN, M.D.,[‡] ERVIN B. PODGORSAK, PH.D.,[*] MARIA WERNER-WASIK, M.D.,[§] ROBERT LUSTIG, M.D.,[||] CHRISTOPHER J. SCHULTZ, M.D.,[¶] WILLIAM SAUSE, M.D.,[#] PAUL OKUNIEFF, M.D.,[**] JAN BUCKNER, M.D.,[††] LUCIA ZAMORANO, M.D.,[‡‡] MINESH P. MEHTA, M.D.,[§§] AND WALTER J. CURRAN, JR., M.D.[§]

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 853–860, 2004

RTOG 93-05 compared then-conventional treatment (radiation and carmustine) with and without upfront SRS boost in patients with GBM <4 cm in diameter & found no difference in survival (13.5 vs. 13.6 months)

SRS for recurrent High-Grade Gliomas

No RCTs comparing radiosurgery to alternative or additional therapies, including repeat surgery, further chemoradiation (standard fractionation), or best supportive care



32-year-old male underwent craniotomy and decompression in 2017 for left frontal high-grade glioma. He received postoperative radiotherapy by 3D Conformal Technique - 5940cGy in 33 fractions with concurrent and adjuvant Temozolomide. 5 years after treatment he underwent revision surgery for recurrence. Histopathology was reported as Astrocytoma grade 4, IDH mutant and he was re-irradiated with Volumetric Modulated Arc Therapy- 25 Gy in 5 fractions.

THANK YOU