International Journal of Radiation Oncology biology • physics

www.redjournal.org

HyTEC Organ-Specific Paper: Brain and Eye

Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Kristin J. Redmond, MD,[*] Chengcheng Gui, BS,[*] Stanley Benedict, PhD,[†] Michael T. Milano, MD,[‡] Jimm Grimm, PhD,[§] J. Austin Vargo, MD,[‖] Scott G. Soltys, MD,[¶] Ellen Yorke, PhD,[#] Andrew Jackson, PhD,[#] Issam El Naqa, PhD,[**] Lawrence B. Marks, MD,[††] Jinyu Xue, PhD,[‡‡] Dwight E. Heron, MD, MBA,[§§] and Lawrence R. Kleinberg, MD[*]

Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; [†]Department of Radiation Oncology, University of California at Davis Comprehensive Cancer Center, Sacramento, California; [‡]Department of Radiation Oncology, University of Rochester, Rochester, New York; [§]Department of Radiation Oncology, Geisinger Medical Center, Danville, Pennsylvania; [‖]Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [¶]Department of Radiation Oncology, Stanford University, Stanford, California; [#]Medical Physics Department, Memorial Sloan Kettering Cancer Center, New York, New York; [**]Department of Machine Learning and Radiation Oncology, Moffitt Cancer Center, Tampa, Florida; [††]Department of Radiation Oncology and the Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill; [‡‡]Department of Radiation Oncology, New York University, New York, New York; and [§§]Department of Radiation Oncology, Bon Secours Mercy Health System, Youngstown, Ohio

Received Oct 7, 2020. Accepted for publication Oct 25, 2020.

Summary

A pooled analysis of manuscripts evaluating tumor control probability for patients treated with stereotactic radiosurgery and fractionated stereotactic radiosurgery for brain

Purpose: As part of the American Association of Physicists in Medicine Working Group on Stereotactic Body Radiotherapy, tumor control probability (TCP) after stereotactic radiosurgery (SRS) and fractionated stereotactic radiosurgery (fSRS) for brain metastases was modeled based on pooled dosimetric and clinical data from published English-language literature.

Methods and Materials: PubMed-indexed studies published between January 1995 and September 2017 were used to evaluate dosimetric and clinical predictors of TCP after SRS or fSRS for brain metastases. Eligible studies had $\geq$10 patients and included detailed dose-fractionation data with corresponding $\geq$1-year local control

Corresponding author: Kristin J. Redmond, MD; E-mail: kjanson3@jhmi.edu

Kristin Redmond and Chengcheng Gui made equal contributions to this study.

Disclosures: K.J.R. reports research support and travel expenses from Elekta AB and Accuray, travel expenses from Brainlab, and data safety monitoring board for BioMimetix. J.G. reports research support from Accuray and Novocure and intellectual property rights for DVH Evaluator. LRK reports research support from Accuray and Novocure. I.E. reports Endectra LLC scientific board membership and grants from the National Institutes of Health. The remaining authors report no disclosures or conflicts of interest.

Data sharing statement: Research data are not available at this time.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2020.10.034.

Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 53–67, 2021
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2020.10.034

metastases was performed. Studies reporting 1-year local control data for at least 10 patients were included in a tumor control probability model. Local control for tumors ≤2.0 cm in a single fraction was 85% for 18 Gy and 95% for 24 Gy. Fractionated regimens should be considered for larger tumors.

(LC) data, typically evaluated as a >20% increase in diameter of the targeted lesion using the pre-SRS diameter as a reference.

Results: Of 2951 potentially eligible manuscripts, 56 included sufficient dose-volume data for analyses. Accepting that necrosis and pseudoprogression can complicate the assessment of LC, for tumors ≤20 mm, single-fraction doses of 18 and 24 Gy corresponded with >85% and 95% 1-year LC rates, respectively. For tumors 21 to 30 mm, an 18 Gy single-fraction dose was associated with 75% LC. For tumors 31 to 40 mm, a 15 Gy single-fraction dose yielded ~69% LC. For 3- to 5-fraction fSRS using doses in the range of 27 to 35 Gy, 80% 1-year LC has been achieved for tumors of 21 to 40 mm in diameter.

Conclusions: TCP for SRS and fSRS are presented. For small lesions ≤20 mm, single doses of ≈18 Gy appear generally associated with excellent rates of LC; for melanoma, higher doses seem warranted. For larger lesions >20 mm, local control rates appear to be ≈ 70% to 75% with usual doses of 15 to 18 Gy, and in this setting, fSRS regimens should be considered. Greater consistency in reporting of dosimetric and LC data is needed to facilitate future pooled analyses. As systemic and biologic therapies evolve, updated analyses will be needed to further assess the necessity, efficacy, and toxicity of SRS and fSRS.

1. Clinical Significance

Approximately 1.5 million individuals receive a diagnosis of cancer in the United States annually, and roughly 20% to 40% of these patients will develop brain metastases.[1] The brain penetration for many chemotherapeutic and targeted agents is limited; thus, radiation therapy (RT) plays an essential role in the management of brain metastases. Conventional radiation treatment fields may be used to deliver radiation to the whole brain. However, numerous studies have demonstrated a relationship between large-field brain RT and both neuropsychological sequelae[2-7] and deterioration in quality of life.[8] Thus, the use of stereotactic radiosurgery (SRS) to treat brain metastases, without whole-brain RT, is increasing.[9]

Recent advances in systemic therapies, including immunologic agents, have improved cancer survival rates (particularly via improved control at extracranial sites). Although some newer agents show improved central nervous system (CNS) penetration, the increasingly long life expectancy after cancer diagnosis and treatment may lead to a rise in late development of brain metastases. Similarly, longer overall survival after oncologic interventions magnifies the importance of minimizing long-term toxicity of therapies both for their quality-of-life implications and for the potential economic and societal ramifications of impaired employment opportunities for patients and caregivers.

Prospective randomized trials have shown equivalent survival outcomes and excellent local control with SRS alone versus SRS plus whole-brain RT in patients with 1 to 4 brain metastases,[2,3,10-12] and an increasing body of both retrospective and prospective observational data indicate similar outcomes in patients with >4 metastases.[13-16] Although treatment of >10 metastases in a single course of therapy remains controversial, small retrospective studies have suggested safety and efficacy of SRS, even in patients with as many as 34 brain metastases.[13,17-22]

Despite the large number of patients treated annually with SRS, there remains controversy and large variability in practice patterns, including the prescribed radiation dose. Radiation Therapy Oncology Group (RTOG) 90-05 was a prospective phase 1 trial that estimated the maximum tolerated dose for single-fraction SRS in patients who were previously treated with partial or whole-brain RT.[23] The researchers reported that single-fraction prescription doses of 24, 18, and 15 Gy for tumors with maximum diameters of ≤2 cm, 2 to 3 cm, and 3 to 4 cm, respectively, were associated with acceptable rates of toxicity at 3 months after SRS; the actuarial rate of necrosis at 2 years was 11%. Although tumor control was not the study's endpoint, the estimated overall infield tumor control rate was ≈50%, with higher control rates in the subset with brain metastases than the primary brain tumor subset.

There have been no reported randomized trials comparing local control after various SRS and fractionated SRS (fSRS) fractionation schemes. More than 1000 relevant retrospective series have been published, but the variability in data quality and reported details limits their potential to guide decision making. Local recurrence of brain metastases can cause morbid neurologic deficits, and the resultant interventions (eg, frequent radiologic evaluations, surgery, and/or additional RT) increase health care costs.

The purpose of this initiative of the American Association of Physicists in Medicine Working Group on Biological Effects of Hypofractioned Radiotherapy/SBRT (WGSBRT) is to review and publish data on Hypofractionated Treatment Effects in the Clinic (HyTEC), providing a detailed, pooled analysis of published data to evaluate dosimetric and clinical predictors of tumor control probability (TCP) and normal tissue complication probability (NTCP) for patients treated with SRS and fSRS for tumors throughout the body. We herein report on the TCP analysis for brain metastases treated with SRS and fSRS, with the

long-term goals of increasing consistency in practice patterns, improving tumor outcomes, and minimizing toxicity.

2. Endpoints

The primary endpoint in this review was local control per metastasis. The definition of local recurrence varied between studies and was not always reported but was most commonly defined according to the response evaluation criteria in solid tumors criteria (>20% increase in diameter of the targeted lesion, using the pre-SRS diameter as a reference). Pathologic verification of intracranial progression of treated metastases was included when available, but the majority of studies did not include these data. Actuarial statistics were used to investigate local control with censoring of data for patients lost to follow-up or dead from disease but without evidence of progressive brain metastases. When available, overall survival was reported on a per-patient basis from the time of SRS treatment. Care is needed when interpreting actuarial data in this setting. Often, the projected local control is computed by censoring patients at the time of death, and the accuracy of actuarial techniques requires that censoring events be independent of the endpoint under consideration. Because the pace of extracranial disease (which can cause the censoring event of death) and the pace of regrowth of treated intracranial disease (which obviously affects local recurrence) are likely related, these estimates may not be accurate and may overstate local control.[24]

3. Challenges Defining Volumes

Although not all studies described physically contouring a target, those that did defined the gross tumor volume (GTV) as the region of contrast enhancement on T1-weighted post-gadolinium magnetic resonance imaging (MRI).

Half of the studies (see Table 1) predominantly included patients treated with a Gamma Knife (GK) (Elekta Medical Systems, Stockholm, Sweden), where targets are delineated directly on a high-resolution MRI. The GK systems that were used in the studies analyzed here used a frame-based stereotactic immobilization, and the target typically encompassed gross disease without a planning target volume (PTV) expansion or aimed at the radiologic abnormality without explicitly delineating a target. Greater local control has been associated with less conformal stereotactic treatment plans.[25,26] Four GK studies included in our analysis used a 1- to 3-mm radial expansion margin from GTV to PTV.

The other half of studies included patients treated on linear accelerator (LINAC)-based systems, robotic systems, or helical tomotherapy, in which the high-resolution T1-weighted post-gadolinium MRI (used for target delineation) is registered to a simulation computed tomography scan. Given minor inaccuracies in image fusion, the possibility of microscopic extension, and the potential for small amounts of patient movement during treatment, half of studies used a radial expansion from GTV to PTV, approximately 20% of studies did not use an expansion, and the remainder did not specify (Table 1).

For all SRS systems, the potential impact of MRI distortion, particularly at the periphery of the cranium, should be recognized. Ultimately, the precision of SRS treatment is multifactorial, varying with different technologies and the level of expertise of the physics and therapy team. Therefore, appropriate PTV expansions should be determined at an institutional level while remembering the fine balance between ensuring full coverage of regions of gross disease and minimizing the target volumes and the risk of radionecrosis.

4. Review of Outcomes Data

Study selection

PubMed was used to identify eligible studies using the following key terms: "SRS and brain metastases," "fractionated stereotactic radiosurgery and brain metastases," "Gamma Knife (GK) and brain metastases," "CyberKnife and brain metastases," "brain metastases and local control," and "brain metastases and dose volume." The literature search was updated most recently in September 2017. All manuscripts identified in this manner were assessed. Similar to the review by Wiggenraad et al that was published in 2011,[27] only studies that reported at minimum 1-year local control rates for each dose and fractionation scheme were included in the analysis. The selection criteria were that the margin prescription dose, fractionation, and tumor size had to be clearly reported with corresponding actuarial local control and/or overall survival at 1 and/or 2 years, with at least 10 patients in each stratified group. Case reports and systematic reviews were eliminated, and in situations in which a single institution published multiple related series, only the most recent update was included.

Search results

The preliminary PubMed search identified 2951 potentially eligible manuscripts. Initial screening revealed that the vast majority of journal articles did not report sufficient detail to be included in a dose-response model. In total, stratified margin dose, fractionation, and size groups of at least 10 patients with associated actuarial 1- and/or 2-year local control and/or overall survival outcomes were included among 56 manuscripts, as summarized in Table 1. These manuscripts included patients with a cumulative 13,929 brain metastases that were included in the HyTEC dose-response models. Of the studies in which the data were available, the most common cancer types were lung cancer, melanoma, renal cell carcinoma, and breast cancer. Of the 28 manuscripts that reported recursive partitioning analysis (RPA) class,[28] the majority of patients were RPA class II.

Table 1 Characteristics of patients in the sample studies

Series	No. of tumors*	GTV-PTV margin (mm)	Additional WBRT	Histology	% RPA class†	Machine	% Male
Chang 2003[31]	153	NR	47.4%	Melanoma 29.6%, NSCLC 28.1%, renal cell 23.7%, breast 8.9%	RPA I 8.1%, RPA II 86.7%, RPA III 5.2%	LINAC	NR
Shehata 2004[32]	468	1	49%	Lung 53%, breast 18%, melanoma 13%	NR	GK	48.1
Vogelbaum 2006[67]	126‡	NR	81%	Lung 44%, breast 19%, melanoma 14%, renal cell 11%	RPA I 22%, RPA II 73%, RPA III 5%	GK	43
Ernst-Stecken 2006[68]	72	3	56.9%	Breast 27%, melanoma 25%, rectal 21%, lung 14%, kidney 6%	NR	LINAC	39
Narayana 2007[73]	22	2-3	0	Lung 35%, melanoma 20%, renal 15%, breast 10%, GI 10%, ovary 5%, sarcoma 5%	NR	LINAC	45
Lutterbach 2008[69]	155	0-2	0	Lung 26.7%, breast 19.8%, renal 14.9%, melanoma 11.9%, GI 11.9%, 5.9% urogenital	RPA I 14.8%, RPA II 64.4%, RPA III 20.8%	LINAC	48.5
Molenaar 2009[33]	150	2	27.9%	Lung 57%, breast 19%, melanoma 13%, colorectal 6%	RPA I 28%, RPA II 69%, RPA III 4%	LINAC	46.5
Higuchi 2009[74]	46	0	0	Colon 32.6%, lung 27.9%, breast 25.6%, kidney 7%, thyroid 2.3%, gastric 2.3%, esophageal 2.3%	RPA I 0%, RPA II 83.7%, RPA III 16.3%	GK	55.8
Koyfman 2010[34]	33	0	51%	NSCLC 44%, renal 19%, breast 16%	NR	GK	37.2
Elliott 2011[35]	255	0	0	Lung 50.5%, breast 19.3%, melanoma 18.4%, renal 6.4%, colon 1.8%	RPA I 15.6%, RPA II 78.9%, RPA III 5.5%	GK	31.2
Kelly 2011[36]	22	0	96%	Lung 33.3%, breast 33.3%, melanoma 12.5%, renal 12.5%	NR	LINAC	41.7
Hatiboglu 2011[37]	60	0	25%	Lung 33%, melanoma 24%, breast 18%, kidney 12%,	RPA I 13%, RPA II 78%, RPA III 9%	LINAC	51.6
Wang 2012[75]	51	2-3	49%	Lung 27%, melanoma 32%, breast 24%, kidney 11%, colon 5%	RPA I 32%, RPA II 68%	CK	51.4
Lin 2012[38]	48	1-2	47%	Breast 33%, NSCLC 28.8%, renal 11%, melanoma 6.6%	RPA I 8.9%, RPA II 64.4%, RPA III 26.6%	LINAC	35.6
Han 2012[76]	80	NR	27.5%	NSCLC 38.8%, colorectal 12.5%, breast 11.3%	RPA I 16.3%, RPA II 45%, RPA III 38.8%	GK	61.3
Grandhi 2012[14]	653	0	88.5%	Melanoma 31.2%, NSCLC 29.5%, breast 24.6%, SCLC 8.2%	RPA I 13.1%, RPA II 75.4%, RPA III 11.5%	GK	55.7
Wiggenraad 2012[77]	111	2	30%	Lung 47%, breast 20%, melanoma 11%,	RPA I 16%, RPA II 79%, RPA III 4%	LINAC	37
Ogura 2012[39]	27	1	100%	Lung 61.9%, breast 14.2%	RPA 1 7%, RPA II 81%, RPA III 11%	LINAC	52.3
Likhacheva 2013[40]	440§	NR	13%	NSCLC 34%, melanoma 29%, breast 16%, renal 8%	RPA I 10%, RPA II 86%, RPA III 4%	GK 89%, LINAC 11%	48.2

(*continued on next page*)

Table 1 (*continued*)

Series	No. of tumors*	GTV-PTV margin (mm)	Additional WBRT	Histology	% RPA class†	Machine	% Male
Mathew 2013[41]	198	0	NR	Melanoma 100%	NR	GK	51.7
Minniti 2013[78]	101	2	0	NSCLC 22.8%, breast 18.8%, colon 5.9%, melanoma 27.8%, renal 17.8%	RPA I 26%, RPA II 63%, RPA III 11%	LINAC	47.5
Kim 2013[42]	64	0	NR	Renal 52.2%, sarcoma 21.7%, melanoma 26%	RPA II 91.3%, RPA III 8.7%	GK	78.3
Baschnagel 2013[43]	337	NR	0	NSCLC 66%, breast 13%, Melanoma 5%, GI 7%, renal 4%	RPA I 8%, RPA II 83%, RPA III 8%	GK	NR
Luther 2013[44]	95	2-3	NR	NR	NR	GK	39.2
Brennan 2014[70]	50	2	NR	NR	NR	LINAC	NR
Tam 2014[45]	86‖	NR	NR	Breast 100%	NR	GK	NR
Feuvret 2014[79]	36	1 for SRS 2 for SRT	0	Lung 53.5%, breast 17%, melanoma 14%, renal 5.5%	RPA I 25%, RPA II 64%, RPA III 11%	LINAC	55
Murai 2014[80]	61	2	0	Lung 56%, GI 25%, breast 8%	RPA I 37%, RPA II 39%, RPA III 24%	CK	68.5
Kilburn 2014[46]	52	0	43.2%	Lung 39%, breast 34%, renal 9%, melanoma 9%	RPA I 11.3%, RPA II 84.1%, RPA III 2.3%	GK	43.2
Nagai 2014[47]	85	2	0	Lung 85%, liver 2%, colon 2%, Breast 7%, cervix 2%	RPA I 13%, RPA II 77.7%, RPA III 9.3%	Tomo	55.6
Minniti 2014[71]	46¶	1-2	0	Breast 47%, NSCLC 35%, colon 6%	NR	LINAC	32.4
Yomo 2014[81]	52	NR	6.9%	Lung 58.6%, breast 12%, colorectal 12%, ovary 3.4%	RPA I 5%, RPA II 46.6%, RPA III 48.3%	GK	63.7
Rades 2014[48]	75#	NR	NRNR	Melanoma 100%	NR	LINAC 81.5%, CK 18.5%	46.3
Zairi 2014[49]	115	NR	0	NSCLC 100%	RPA I 30.3%, RPA II 47.2%, RPA III 22.5%	GK	78.7
Tamari 2015[50]	109	1	16.4%	NSCLC 96%, SCLC 4%	NR	CK	69
Voong 2015[51]	77	1	16	NR	NR	GK	50
DeAzevedo Santos 2015[52]	116	1	44%	Breast 32%, lung 30%, melanoma 26%	NR	LINAC	37
Ebner 2015[82]	93	1-2	NR	Breast 17.2%, melanoma 14%, NSCLC 48.4%	NR	GK	41
Barra 2015[53]	46	3	7%	Lung 40%, breast 33%, kidney 7%, ovary 7%, melanoma 7%, cervix 3%, colon 3%	NR	Tomo	53.3
Zimmerman 2016[30]	164	0	NR	NSCLC 34%, SCLC 10%, radioresistant 33%, breast 14%	RPA I 7.3%, RPA II 75%, RPA III 17.7%	GK	52
Navarria 2016[72]	102	3	NR	Breast 17%, NSCLC 56%, melanoma 12%	RPA I 18%, RPA II 79%, RPA III 3%	LINAC	61.7
Specht 2016[83]	26	3	NR	NR	NR	LINAC	41.3

(*continued on next page*)

Table 1 (*continued*)

Series	No. of tumors*	GTV-PTV margin (mm)	Additional WBRT	Histology	% RPA class†	Machine	% Male
Ishihara 2016[54]	138	1	7.6%	Lung 100%	RPA I 24.6%, RPA II 41.5%, RPA III 33.9%	LINAC	73.6
Joshi 2016[55]	51		40%	NSCLC 54%, breast 21%, GI 11%, SCLC 8%	NR	GK	41.7
Ahmed 2016[56]	314	1	NR	Melanoma 100%	NR	LINAC	62.5
Yomo 2016[57]	245	NR	0	Lung 69.8%, GI 15.1%, melanoma 2.8%, breast 1.9%, kidney 1.9%, thyroid 1.9%	RPA II 52.8%, RPA III 47.2%	GK	65.1
Lima 2017[84]	37	2	NR	NR	NR	LINAC	46.3
Wolf 2018[58]	1237	NR	13.5%	NSCLC 48%, melanoma 20%, breast 17.5%, GI 3.5%, renal 1%	NR	GK	39
Mohammadi 2017[59]	2410	NR	38%	NSCLC 44%, breast 19%, renal 14%, melanoma 11%, SCLC 5%	RPA I 16%, RPA II 79%, RPA III 5%	GK	44
Trifiletti 2017[60]	1596	0	24%	NSCLC 25.3%, breast 11.9%, melanoma 36.2%, renal 4.2%,GI 5.7%	NR	GK	50.7
Murray 2017[61]	27	2	65.6%	Breast 27.3%, NSCLC 31.8%, Gyn 13.6%, melanoma 6.8%, renal 4.5%, colorectal 4.5%	NR	GK	36.4
Miller 2017[62]	864	NR	54%	Breast 100%	NR	GK	
Miller 2017[63]	1751	NR	57%	NSCLC 100%	NR	LINAC and GK	54%
Choi 2017[64]	19	0	NR	NSCLC 100%	NR	CK 88%, LINAC 12%	58.8
Mahajan 2017[65]	58	1	NR	NR	NR	GK	58.7
Koffer 2017[66]	24	NR	NR	NSCLC 41%, SCLC 18%, colon 14%, breast 9%, renal 9%, endometrial 5%, esophageal 5%	NR	GK	27.3

Abbreviations: CK = cyberknife; GI = gastrointestinal; GK = Gamma Knife; GTV = gross target volume; LINAC = linear accelerator–based system; N = number of brain metastases; NR = not reported; NSCLC = non-small cell lung cancer; PTV = planning target volume; RPA = recursive partitioning analysis; SCLC = small cell lung cancer; Tomo = helical tomotherapy; WBRT = percent of patients receiving whole brain radiation therapy either before or within 1 month of stereotactic radiosurgery.

* The number of tumors with follow-up is used to weight the data points in the model.

† In the context of clinical use, RPA is a statistical method that produces a decision tree describing associations between dichotomized parameters and an outcome of interest (in this case, median overall survival). In this context, RPA class 1 is defined as patients with Karnofsky performance status $\geq$70, <65 years of age, with a controlled primary and no extracranial disease; class 3 is defined as patients with KPS <70; and class 2 includes all others.[28]

‡ Cleveland Clinic results for small tumors were published again more recently, so only the 85 medium and 41 large tumors from Vogelbaum (2006)[67] were used in the models, and instead of the 249 small tumors from Vogelbaum (2006),[67] we modeled the small tumors from Mohammadi (2017)[59] and Miller (2017).[62,63]

§ An approximate weighting of 440 small tumors was inferred from the ratio of 1-year local control for tumors larger and smaller than 2 cm^3, as compared to the overall 1-year local control; Table 2 in the paper (ref 40) confirms that half of the patients had total tumor volume much less than the small-tumor threshold of 4.2 cm^3.

‖ The median number of lesions among 57 patients was 2; therefore, at least half of the patients had 2 tumors, and the total number of tumors in this study was 86. Because the actual number was not provided, we used 86 as a conservatively low weighting for the model.

¶ At least 46 tumors in 34 patients. We used 46 as a conservatively low weighting for the model.

At least 75 tumors in 54 patients.

The median GTV to PTV expansion was 1 mm (range, 0-3 mm). The median prescription dose was 20 Gy in a single fraction (range, 13-32 Gy in 1-5 fractions). Half of the studies used predominantly GK and the remainder used LINAC-based systems, robotic systems, and helical tomotherapy. The median prescription isodose line was inconsistently reported, but because we analyzed dose to the PTV margin, this did not limit our analysis. In approximately half of the studies, a median of 44% (range, 6.9%-100%) of patients received whole brain radiation therapy (WBRT) either before or within 1 month of SRS.

Data extraction

Primary data extraction and subsequent quality assurance reviews were performed by 3 investigators (J.G., C.G., and K.R.). One-year local control, median prescription dose to the PTV margin, and number of fractions were collected from all eligible studies per metastatic lesion. When available, 2-year local control was similarly documented per metastasis. In addition, the following data were charted in aggregate for each study when available: first author and institution, manuscript year, treatment technology and technique, number of patients, and median, 1-year, and 2-year overall survival from the time of SRS. Patient characteristics including sex, brain metastasis RPA class,[28] primary tumor histology, number of brain metastases, and prior WBRT were recorded. Tumor parameters including lesion diameter or volume and GTV-PTV expansion were also noted.

5. Factors Affecting Outcomes

Data from included studies were tabulated per metastatic lesion. Analyses were performed to examine factors potentially contributing to local control, including brain metastasis volume, total dose, and number of fractions. Given that outcomes were generally not stratified by histology, we were unable to evaluate the impact of primary tumor histology in the overall analyses. However, independent analyses were performed for melanoma. Tumors were defined by RTOG 90-05 maximum diameter size criteria as follows: $\leq$20 mm, small; 21 to 30 mm, medium; and 31 to 40 mm, large. In the case of studies that did not present results stratified by RTOG 90-05 size criteria, median tumor size was extrapolated to the overall cohort. Other data that were collected but not accounted for in the analyses included RPA class,[28] prior treatment with WBRT, systemic therapy, sex, treatment technology, and expansion from GTV to PTV.

6. Mathematical/Biological Models

Our searches identified only 2 groups that modeled data from pooled studies: Wiggenraad et al[27] and Shuryak et al.[29] Of 1500 articles published on radiosurgery for brain metastases in radiation-naïve patients and patients previously treated with WBRT up to 2011, the Wiggenraad 2011 review only included 12 data points from 11 papers in the dose-response model. As can be seen from Table 1[14,30-84] and Tables EA1 to EA3, our literature search confirmed the small number of reports that provided sufficient stratification of dose, fractionation, and size to be modeled; we only found 2 additional usable data points from that period.

All dose-response models in this HyTEC review were logistic[85] (Table EA4). To address the question of the most appropriate value for α/β in the dose-response model, logistic models were generated from the physical dose for each fractionation and compared across fractionations. Ninety-nine percent of the usable published data for small tumors were for single-fraction SRS, so it was not possible to reliably estimate α/β from these data. Instead, data for medium to large tumors were combined. In all figures, the full dots surrounded by a circle represent single-fraction data, the diamonds represent data from 2- to 5-fraction SRS, and the diameter of the symbol is loosely proportional to the number of cases in each data point. Figure 1 shows only raw physical dose data. It is apparent that 18 Gy in 1 fraction (Fig. 1A) had similar reported outcomes to 24 Gy in 3 fractions (Fig. 1B), which suggests an $\alpha/\beta \approx 22$ Gy in the linear quadratic model. Isoeffective comparisons of dose response in these data result in even higher α/β values, and maximum-likelihood parameter searches in these data also resulted in $\alpha/\beta \geq 20$ Gy. For simplicity, we used $\alpha/\beta = 20$ Gy throughout the rest of this analysis.

Composite models including all analyzed fractionations for local control and overall survival are shown in Figures 2 and 3 (using the model parameters in Table EA4), respectively, stratified by RTOG 90-05 criteria for small, medium, and large size. Greater than 85% and 95% 1-year local control for small tumors was achieved with a minimum prescription dose of 18 Gy and 24 Gy, respectively (Fig. 2A). The RTOG 90-05 maximum tolerated doses of 18 Gy in a single fraction for medium-sized tumors was associated with 75% local control in patients with medium-sized metastases (Fig. 2B), and a single fraction of 15 Gy in large tumors yielded approximately 69% local control (Fig. 2C). When including published data on 2 to 5 fractions, 80% 1-year local control of medium and large tumors was achieved with single-fraction equivalent doses of 19.6 Gy and 21.4 Gy, respectively, using the linear quadratic model and an α/β of 20 Gy. The fractionation benefit was most evident for 2-year local control of large tumors (Fig. 2F), which did not exceed 60% in the single-fraction studies, although 7 of 8 fractionated data points exceeded 60% ($P = .0014$).

Overall survival must be interpreted with caution in the context of brain metastases because it is often driven predominantly by extracranial factors. Indeed, only 2 of the randomized studies reported a survival advantage associated with an intervention for brain metastases,[86,87] whereas the remainder detected differences in local control but not overall survival.[2,10,88,89] With that limitation in mind, it is interesting to note that overall survival at 1 year exceeded

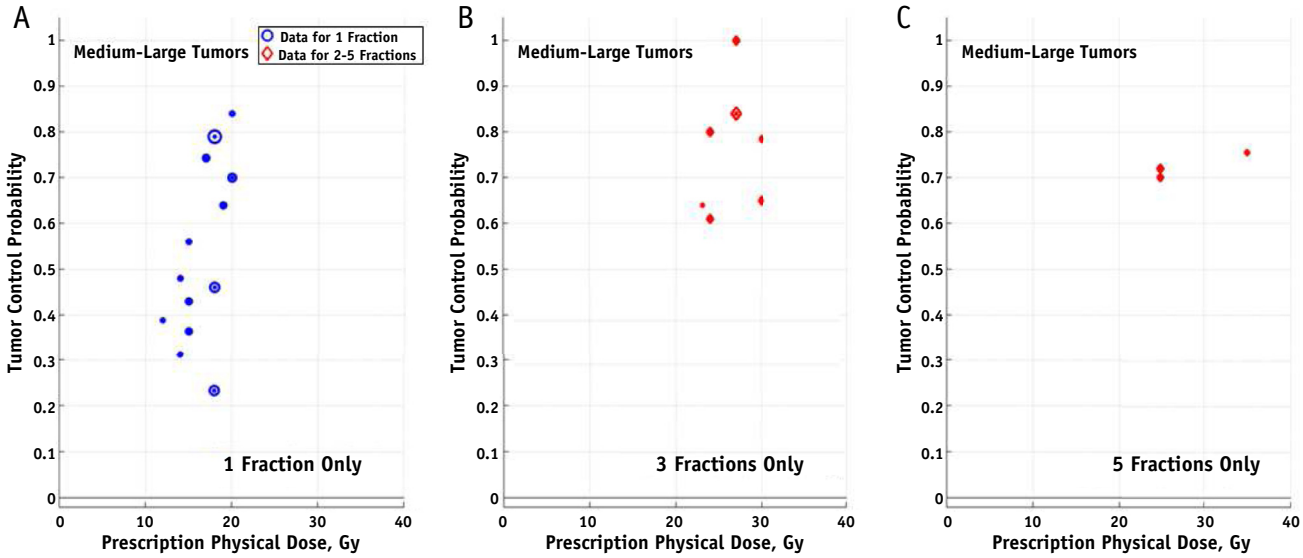

Fig. 1. Logistic models in physical dose (Gy) to evaluate α/β for 2-year local control (A-C) for medium to large tumors. Note that the dose is the reported prescribed dose to the planning target volume margin.

50% for only 17 of the 48 data points for which it was reported (Fig. 3A-3C). However, with modern systemic agents including targeted therapies and immunotherapy, this is expected to improve; indeed, all except 2 of these 17 data points with higher overall survival were published in the past 5 years ($P = .026$). Nine of 35 single-fraction data points had >50% 1-year overall survival, compared with 8 of 13 fractionated data points ($P = .039$).

Melanoma metastases had the steepest dose response, with single-fraction doses of 18 Gy and 24.6 Gy having estimated local control rates at 1 year of 19.5% and 95%, respectively (Fig. 4). In the 4 usable studies that included only melanoma metastases, all tumors were in the small category, and all were treated in a single fraction.

The median prescribed dose among all of the single-fraction data was 20 Gy. A simple way to compare the expected effects of fractionation on the therapeutic ratio, and the assumed α/β value, is shown in Table 2. If $\alpha/\beta = 10$ Gy, then 20 Gy in 1 fraction would be an linear quadratic equivalent to 30 Gy in 3 fractions and 35 Gy in 5 fractions. However, if $\alpha/\beta = 20$ Gy, then these 3-fraction and 5-fraction regimens would effectively have an 8% and 11.5% higher single-fraction equivalent dose, respectively. Furthermore, given a nominal $\alpha/\beta = 2$ Gy for normal brain, the effective single-fraction equivalent dose to normal brain would be 10% and 16% lower than the tumor equivalent dose for the 3-fraction and 5-fraction regimens, respectively. For convenience, this comparison is made for several common brain metastases radiosurgery schedules in Table 3, along with the modeled 2-year actuarial local control rates, sorted by biologically effective CNS critical structure dose. The raw data are provided in Tables EA1 to EA3.

7. Special Situations

The studies in the present review addressed SRS in the setting of intact metastases and might not be applicable to the postoperative setting. There was a paucity of studies reporting outcomes specific to postoperative tumor beds, so a separate TCP analysis for this subset of lesions was not possible. Care should be taken in applying the recommendations of the present study to the postoperative setting. It is important to note that a recent randomized controlled study suggests lower local control after SRS to the tumor bed compared with postoperative WBRT.[88] Given that higher biologically equivalent doses are used in SRS than in WBRT, one may speculate that current recurrence patterns may be driven by inaccuracies in target delineation, including margin, rather than by insufficient dose. Future studies investigating TCP in the postoperative setting will be important once optimal target delineation for this intervention is more thoroughly understood.

The present analysis included studies with SRS alone (ie, without concurrent systemic therapy). Given the increasing number of systemic agents available for patients with metastatic disease, it is increasingly common for patients to be referred for consideration of SRS for new/progressive brain metastases while the patient is taking systemic therapy that appears to be efficacious for the extracranial disease. In this situation, one might be reluctant to hold the systemic therapy during SRS. It is possible that synergies between the SRS and the systemic therapy might alter the therapeutic ratio of SRS and/or the dose/volume/response relationship.

Finally, the studies included in this analysis predominantly enrolled adult patients. Therefore, it remains unclear whether they are directly applicable to pediatric patients.

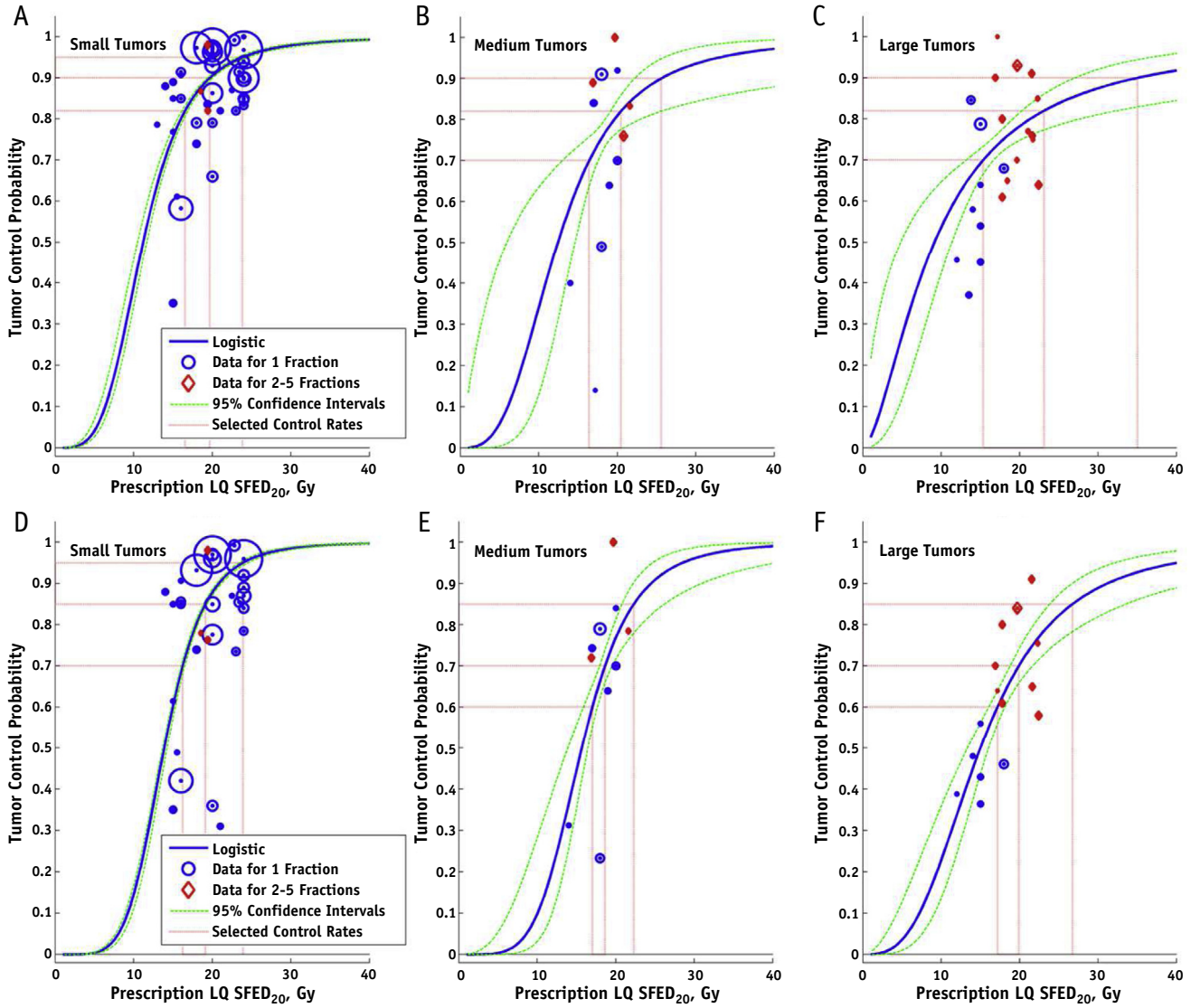

Fig. 2. Logistic models in single-fraction equivalent dose (Gy) with $\alpha/\beta = 20$ Gy, for 1-year local control (A-C) and 2-year local control (D-F), stratified by small, medium, and large tumor size. Note that dose is based on the reported prescribed dose to the planning target volume margin.

8. Recommended Dose/Volume Objectives

RTOG 90-05 was a landmark prospective dose escalation study that enrolled patients with recurrent primary brain tumors and brain metastases.[23] All patients had received prior cranial radiation to median doses of 60 Gy and 30 Gy, respectively. The maximum tolerated dose (MTD) was estimated to be 24 Gy, 18 Gy, and 15 Gy for tumors $\leq$20 mm, 21 to 30 mm, and 31 to 40 mm, respectively. By contrast, it is important to note that although the current study recorded treatment with previous WBRT in a binary fashion, the TCP analyses presented in this manuscript do not account for the cumulative effect of prior RT exposure.

For small tumors (ie, $\leq$20 mm), the current analysis suggests that lower prescription doses (eg, 18 Gy) are generally associated with excellent local control. In patients with small melanoma metastases, higher doses may be beneficial, with 90% local control associated with a single-fraction dose of 23.4 Gy.

For medium-sized lesions (ie, 20-30 mm), the current analysis suggests that 18 Gy in a single fraction (ie, the MTD from RTOG 90-05) is associated with a local control rate of approximately 75%. Similarly, for larger lesions (ie, $>$30 mm), the current analysis suggests that 15 Gy in a single fraction (ie, the MTD from RTOG 90-05) is associated with a local control rate of approximately 69%.

For both medium and larger lesions (ie, $>$20 mm), higher rates of local control (eg, $>$80%-90%) may require single doses that may be associated with increased rates of radionecrosis, according to RTOG 90-05. Therefore, fractionated treatment regimens such as 30 Gy in 3 fractions or 35 Gy in 5 fractions could be considered in these patients. Interestingly, the current analyses suggests potentially

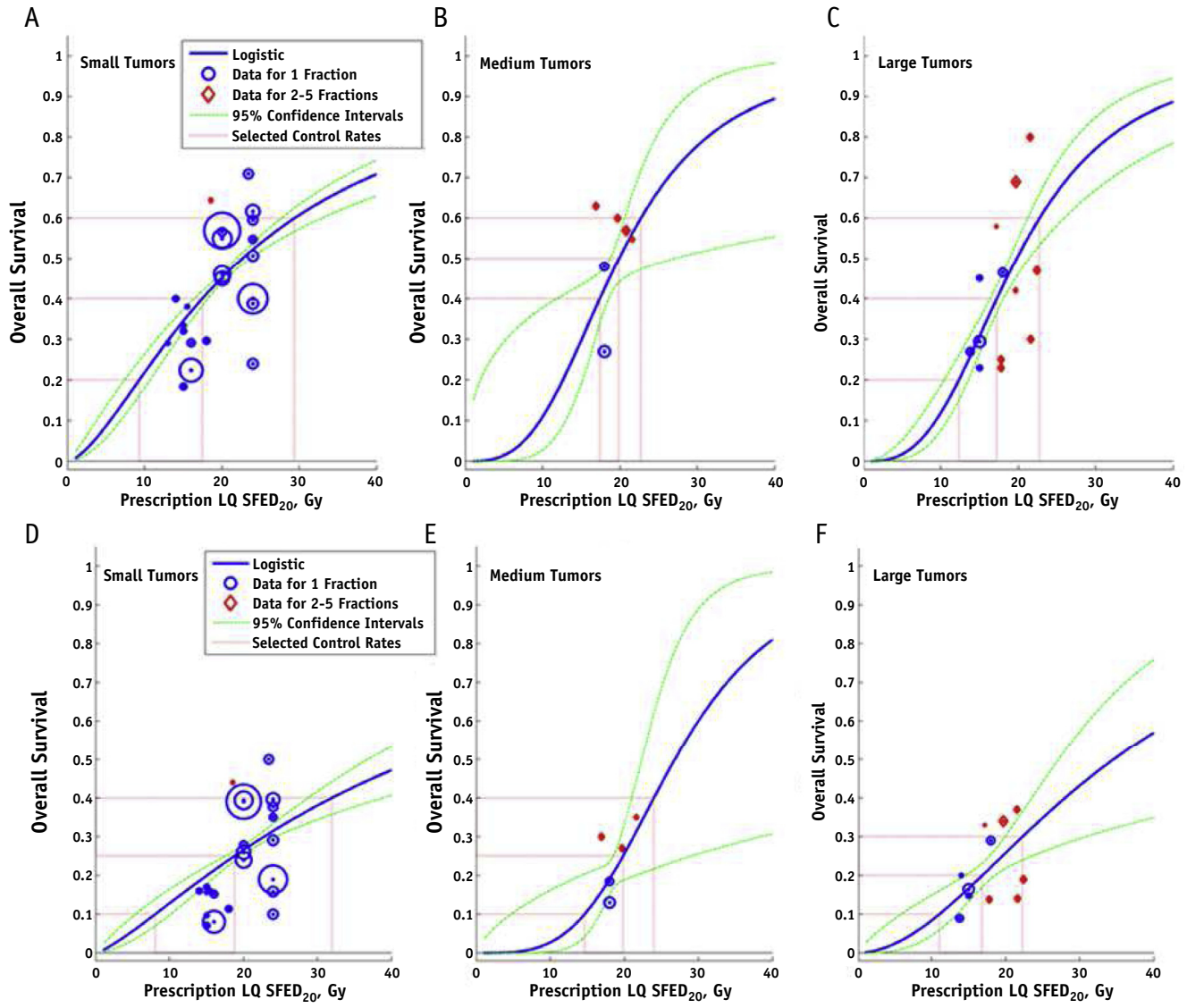

Fig. 3. Logistic models in single-fraction equivalent dose (Gy) with $\alpha/\beta = 20$ Gy, for 1-year overall survival (A-C) and 2-year overall survival (D-F), stratified by small, medium, and large tumor size. Note that dose is based on the reported prescribed dose to the planning target volume margin. These data should be interpreted with caution. The relationship between overall survival and interventions for brain metastases is controversial given that it is often driven predominantly by extracranial factors.

higher rates of local control with fractionated treatment regimens compared with single-fraction treatment. This is consistent with prior data reporting superior 1-year local control after 27 Gy in 3 fractions compared with single-fraction doses of 18 Gy for metastases of 2 to 3 cm in size and 15 to 16 Gy for metastases >3 cm.[90] However, these results should be interpreted with caution; given the paucity of pathologic confirmation of active disease in this population, the higher local control with fractionation may simply represent reduced pseudoprogression, as may be seen on MRI even years after RT.[91]

9. Future Studies

This in-depth TCP analysis of the 56 studies currently available in the literature reaffirms the efficacy of SRS and fSRS in the management of brain metastases, with modeled 1-year local control rates of 95%, 75%, and 69% for small, medium, and large brain metastases, respectively. Although we incorporated the best-quality and up-to-date published data available, the majority of studies in our model are retrospective in nature and thereby limited in accuracy for

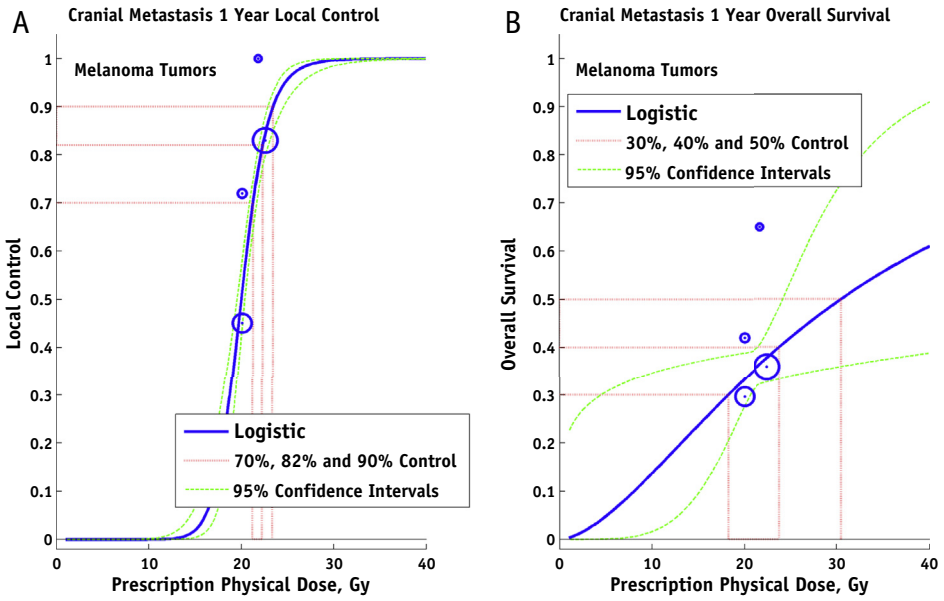

Fig. 4. Logistic models in physical dose (Gy) for 1-year local control (A) and 1-year overall survival (B) for patients with melanoma metastases treated with a single fraction. Note that dose is based on the prescribed dose to the planning target volume margin.

the reasons noted. Future high-quality prospective studies will be essential to better understand the optimal radiation prescription dose (eg, minimum and maximum doses, prescription isodose line, and target coverage) that will maximize local control while minimizing toxicity. In addition, prospective data might allow us to compare different methods of target delineation.

Future studies might consider the following variables that could not be fully studied in the present analysis.

Prescription isodose line

The TCP analyses performed in this study focused on the SRS prescription dose to the PTV margin. Few studies reported the prescription isodose line, which may range typically from 50% in patients treated with GK to 80% to 90% for patients treated using LINAC-based systems. This equates to dramatically different maximum doses received by tumors. Given the paucity of data reported in the literature summarized in this manuscript, these analyses did not account for maximum doses or prescription isodose line. However, future dose-response analyses using data from individual metastatic lesions will be important to better evaluate for the impact of dose-volume effects.

Table 2 Single-fraction equivalent dose as a function of α/β, linear quadratic model*

	Single-fraction equivalent dose for 20 Gy in 1 fraction	Single-fraction equivalent dose for 30 Gy in 3 fractions	Single-fraction equivalent dose for 35 Gy in 5 fractions
$\alpha/\beta = 2$ Gy	20	18	16.8
$\alpha/\beta = 10$ Gy	20	20	20
$\alpha/\beta = 20$ Gy	20	21.6	22.3

* Time not considered.

PTV margins

The PTV expansions used in the articles reviewed for this study were variable, ranging from 0 to 3 mm. It is important to emphasize that these variable expansions can have a large impact on the actual dose received by the GTV, given the steep, relatively isotropic radiation dose fall-off with SRS. For example, 18 or 20 Gy prescribed to a target with a 2-mm expansion may be comparable to the dose received with a prescription of 24 Gy prescribed to a target with no margin. Future studies might evaluate the relationship of rates of control and necrosis to PTV margins.

Histology

Our analyses did not account for tumor histology except for the analysis of small melanoma metastases, in which a steep dose-response was observed (Fig. 4). The literature consistently suggests that rates of local control with SRS are similar for tumors that are traditionally considered to have different levels of radiosensitivity with conventional fractionation, perhaps owing to activation of alternative pathways of cell kill, such as apoptosis after SRS. However, TCP analyses for individual metastases, stratified by histology, are not feasible with a pooled analysis of the current literature. The opportunity for these types of analyses will

Table 3 Common prescription schemes, associated single-fraction equivalent doses, and modeled actuarial 2-year local control rates*

No. of fractions	Total physical dose (Gy)	Biologically effective tumor single-fraction equivalent dose (Gy)† $\alpha/\beta = 20$ Gy	CNS critical structure single-fraction equivalent dose (Gy)† $\alpha/\beta = 2$ Gy	Modeled actuarial 2-year local control		
				Small (≤20 mm)	Medium (21-30 mm)	Large (31-40 mm)
1	24	24	24	95%		
1	22	22	22	92%	84%	
1	20	20	20	88%	77%	70%
1	18	18	18	80%	66%	63%
3	30	21.6	18	92%	84%	75%
5	37.5	23.6	17.9	95%	88%	80%
5	35	22.3	16.8	93%	85%	77%
3	27	19.7	16.3	87%	75%	69%
1	15	15	15	60%	47%	47%
3	24	17.8	14.5	79%	65%	63%
5	30	19.7	14.5	87%	75%	69%
1	14	14	14		41%	41%
3	21	15.8	12.8		53%	53%
5	25	16.9	12.3		59%	59%
1	12	12	12			34%
3	18	13.8	11			44%

Abbreviations: CNS = central nervous system; SFED = single-fraction equivalent dose.
* Time not considered.
† Calculated based on the linear quadratic model with $\alpha/\beta = 20$ Gy for tumor and $\alpha/\beta = 2$ Gy for CNS normal tissue.

require more consistent reporting of local control based on dose and fractionation for specific tumor histologies.

Methods to score local control

Our analyses depended on the definition of local control applied in each included study, which was defined in many studies by MRI findings rather than pathology. Therefore, it is possible that results were confounded by pseudoprogression, in which irradiated brain metastases experience transient increases in gadolinium enhancement and surrounding T2 fluid-attenuated inversion recovery after SRS that can mimic true progression radiographically and may occur even years after treatment.[91] In addition, the definition of local control varied dramatically between studies; for example, some studies defined recurrence as any increase in size on imaging without confirmation from follow-up studies, whereas other studies used more modern criteria from Response Assessment in Neuro-Oncology[92] or mandated follow-up scans or pathologic confirmation to rule out pseudoprogression. These factors may have led to an artificially high reported rate of local progression, with patients with pseudoprogression incorrectly recorded as experiencing true progression. Conversely, the use of actuarial techniques to compute the estimated local control rate may overstate the control rate.[24] More consistent definitions of progression, incorporation of advanced imaging modalities, and more prospective studies are needed to better understand the impact of different definitions of local failure on the reported rates of local control.

Prior WBRT

Although we recorded treatment with previous WBRT in a binary fashion, the TCP analysis presented here does not account for the cumulative effect of prior RT exposure. Interestingly, it is unclear whether WBRT would improve control by adding additional dose or if tumors that fail WBRT are biologically more aggressive and may benefit from additional dose escalation. These types of analyses are not possible given the current reporting of these data in the literature. More consistent and detailed per-patient reporting of prior WBRT treatment would facilitate such analyses.

As advances in cancer biology and drug development lead to increased administration of systemic and biologic agents with improved CNS penetration, it will be important to continue to investigate the interplay with SRS in terms of necessity, efficacy, and toxicity. It is imperative that radiation oncologists remain intimately involved in clinical trial developments that intertwine brain SRS and novel systemic therapies to ensure incorporation of detailed target delineation and dosimetric parameters as well as consistent and reliable definitions of local control.

10. Reporting Standards for Outcomes

Although nearly 3000 potentially eligible manuscripts exploring SRS and fSRS for brain metastases have been published and indexed in PubMed, only 56 met the basic eligibility criteria for inclusion in this study. This highlights the historical inconsistency in reporting of relevant

information across the literature and the importance of more systematic inclusion of data in the future. Specifically, improved analyses of TCP would be feasible if future publications more regularly report individual dose and fractionation data, preferably per patient, but at a minimum per group of patients. At a minimum, the following should be included for each dose/fractionation schedule:

- Prior WBRT dose and time interval between courses of RT
- Prescription dose and outcome for specific tumor histologies
- Method of target delineation
- PTV expansion
- Immobilization and image guidance
- Tumor size (preferably grouped by RTOG 90-05 criteria)
- Number of metastases treated in each session, as well as details specific to each lesion
- Treatment planning software or dose calculation algorithms used
- Dose delivery platform (ie, treatment machine)
- Maximum and minimum peripheral doses to target
- Percentage of isodose lines covering percentage of GTV and PTV
- Accompanying systemic agents and their timing relative to RT

Reporting of tumor and target volume information per patient would be highly beneficial, preferably as an appendix with full dose-volume histogram data.

If alternative criteria for important data elements are proposed, results should be reported in terms of both the old and the revised standards. The most common example we observed is that many reports stratified outcomes by size criteria other than RTOG 90-05, but because so many reports used different size criteria, there was no way to pool the data.

Consistent definitions of local control are similarly imperative. The Response Assessment in Neuro-Oncology working group for brain metastases has been established[92] in an attempt to develop consensus criteria to differentiate pseudoprogression from progression. However, guidelines are pending. Advanced imaging studies such as magnetic resonance spectroscopy, perfusion- and diffusion-weighted imaging, amide proton transfer imaging, and positron emission tomography−MRI may facilitate improved noninvasive differentiation of pseudoprogression from progression. Similarly, cerebrospinal fluid or serum biomarkers are under development and may play a critical role in future evaluations of tumor control. Nonetheless, at present, pathologic confirmation of active disease remains the gold standard (or, when surgical intervention is not appropriate, serial MRI imaging may be used), with the date of progression backdated to the time of the first radiographic change. In this context, reporting of consistent and reliable follow-up intervals is essential.

References

1. Patchell RA. The management of brain metastases. *Cancer Treat Rev* 2003;29:533-540.
2. Aoyama H, Shirato H, Tago M, et al. 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.
3. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol* 2009; 10:1037-1044.
4. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989;39:789-796.
5. Welzel G, Fleckenstein K, Schaefer J, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *Int J Radiat Oncol Biol Phys* 2008;72:1311-1318.
6. Fisher B, Seiferheld W, Schultz C, et al. Secondary analysis of radiation therapy oncology group study (RTOG) 9310: An intergroup phase II combined modality treatment of primary central nervous system lymphoma. *J Neurooncol* 2005;74:201-205.
7. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2006;24:4570-4574.
8. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008;71:64-70.
9. Trifiletti DM, Sheehan JP, Grover S, et al. National trends in radiotherapy for brain metastases at time of diagnosis of non-small cell lung cancer. *J Clin Neurosci* 2017;45:48-53.
10. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29:134-141.
11. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: Individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2015;91:710-717.
12. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (alliance): A phase III randomized trial of whole brain radiation therapy (WRBT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J Clin Oncol* 2015;33:(supp; abstr LBA4).
13. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys* 2006;64:898-903.
14. Grandhi R, Kondziolka D, Panczykowski D, et al. Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases. *J Neurosurg* 2012;117:237-245.
15. Hunter GK, Suh JH, Reuther AM, et al. Treatment of five or more brain metastases with stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;83:1394-1398.
16. Mohammadi AM, Recinos PF, Barnett GH, et al. Role of gamma knife surgery in patients with 5 or more brain metastases. *J Neurosurg* 2012; 117(Suppl):5-12.
17. Kim CH, Im YS, Nam DH, Park K, Kim JH, Lee JI. Gamma knife radiosurgery for ten or more brain metastases. *J Korean Neurosurg Soc* 2008;44:358-363.
18. Chang WS, Kim HY, Chang JW, Park YG, Chang JH. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: Is stereotactic radiosurgery effective for multiple brain metastases? *J Neurosurg* 2010;113(Suppl):73-78.
19. Lee CK, Lee SR, Cho JM, Yang KA, Kim SH. Therapeutic effect of gamma knife radiosurgery for multiple brain metastases. *J Korean Neurosurg Soc* 2011;50:179-184.

20. Rava P, Leonard K, Sioshansi S, et al. Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery. *J Neurosurg* 2013;119:457-462.
21. Salvetti DJ, Nagaraja TG, McNeill IT, Xu Z, Sheehan J. Gamma knife surgery for the treatment of 5 to 15 metastases to the brain: Clinical article. *J Neurosurg* 2013;118:1250-1257.
22. 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.
23. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291-298.
24. Gelman R, Gelber R, Henderson IC, et al. Improved methodology for analyzing local and distant recurrence. *J Clin Oncol* 1990;8:548-555.
25. Soltys SG, Adler JR, Lipani JD, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys* 2008;70:187-193.
26. Garsa AA, Badiyan SN, DeWees T, et al. Predictors of individual tumor local control after stereotactic radiosurgery for non-small cell lung cancer brain metastases. *Int J Radiat Oncol Biol Phys* 2014;90:407-413.
27. Wiggenraad R, Verbeek-de Kanter A, Kal HB, Taphoorn M, Vissers T, Struikmans H. Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. *Radiother Oncol* 2011;98:292-297.
28. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;37:745-751.
29. Shuryak I, Carlson DJ, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients. *Radiother Oncol* 2015;115:327-334.
30. Zimmerman AL, Murphy ES, Suh JH, et al. Treatment of large brain metastases with stereotactic radiosurgery. *Technol Cancer Res Treat* 2016;15:186-195.
31. Chang EL, Hassenbusch SJ 3rd, Shiu AS, et al. The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery* 2003;53:272-280; discussion 280-281.
32. Shehata MK, Young B, Reid B, et al. Stereotatic radiosurgery of 468 brain metastases $<$ or $=$2 cm: Implications for SRS dose and whole brain radiation therapy. *Int J Radiat Oncol Biol Phys* 2004;59:87-93.
33. Molenaar R, Wiggenraad R, Verbeek-de Kanter A, Walchenbach R, Vecht C. Relationship between volume, dose and local control in stereotactic radiosurgery of brain metastasis. *Br J Neurosurg* 2009;23:170-178.
34. Koyfman SA, Tendulkar RD, Chao ST, et al. Stereotactic radiosurgery for single brainstem metastases: The Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 2010;78:409-414.
35. Elliott RE, Rush SC, Morsi A, et al. Local control of newly diagnosed and distally recurrent, low-volume brain metastases with fixed-dose (20 Gy) gamma knife radiosurgery. *Neurosurgery* 2011;68:921-931; discussion 931.
36. Kelly PJ, Lin YB, Yu AY, et al. Linear accelerator-based stereotactic radiosurgery for brainstem metastases: The Dana-Farber/Brigham and Women's Cancer Center experience. *J Neurooncol* 2011;104:553-557.
37. Hatiboglu MA, Chang EL, Suki D, Sawaya R, Wildrick DM, Weinberg JS. Outcomes and prognostic factors for patients with brainstem metastases undergoing stereotactic radiosurgery. *Neurosurgery* 2011;69:796-806; discussion 806.
38. Lin CS, Selch MT, Lee SP, et al. Accelerator-based stereotactic radiosurgery for brainstem metastases. *Neurosurgery* 2012;70:953-958; discussion 958.
39. Ogura K, Mizowaki T, Ogura M, et al. Outcomes of hypofractionated stereotactic radiotherapy for metastatic brain tumors with high risk factors. *J Neurooncol* 2012;109:425-432.
40. Likhacheva A, Pinnix CC, Parikh NR, et al. Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013;85:656-661.
41. Mathew M, Tam M, Ott PA, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. *Melanoma Res* 2013;23:191-195.
42. Kim H, Jung TY, Kim IY, Jung S, Moon KS, Park SJ. The usefulness of stereotactic radiosurgery for radioresistant brain metastases. *J Korean Neurosurg Soc* 2013;54:107-111.
43. Baschnagel AM, Meyer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with gamma knife surgery. *J Neurosurg* 2013;119:1139-1144.
44. Luther N, Kondziolka D, Kano H, et al. Predicting tumor control after resection bed radiosurgery of brain metastases. *Neurosurgery* 2013;73:1001-1006; discussion 1006.
45. Tam M, Narayana A, Raza S, et al. Role of HER2 status in the treatment for brain metastases arising from breast cancer with stereotactic radiosurgery. *Med Oncol* 2014;31:832.
46. Kilburn JM, Ellis TL, Lovato JF, et al. Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: Is there a volume threshold for toxicity? *J Neurooncol* 2014;117:167-174.
47. Nagai A, Shibamoto Y, Yoshida M, Wakamatsu K, Kikuchi Y. Treatment of single or multiple brain metastases by hypofractionated stereotactic radiotherapy using helical tomotherapy. *Int J Mol Sci* 2014;15:6910-6924.
48. Rades D, Sehmisch L, Huttenlocher S, et al. Radiosurgery alone for 1-3 newly-diagnosed brain metastases from melanoma: Impact of dose on treatment outcomes. *Anticancer Res* 2014;34:5079-5082.
49. Zairi F, Ouammou Y, Le Rhun E, et al. Relevance of gamma knife radiosurgery alone for the treatment of non-small cell lung cancer brain metastases. *Clin Neurol Neurosurg* 2014;125:87-93.
50. Tamari K, Suzuki O, Hashimoto N, et al. Treatment outcomes using CyberKnife for brain metastases from lung cancer. *J Radiat Res* 2015;56:151-158.
51. Voong KR, Farnia B, Wang Q, et al. Gamma knife stereotactic radiosurgery in the treatment of brainstem metastases: The MD Anderson experience. *Neurooncol Pract* 2015;2:40-47.
52. de Azevedo Santos TR, Tundisi CF, Ramos H, et al. Local control after radiosurgery for brain metastases: Predictive factors and implications for clinical decision. *Radiat Oncol* 2015;10:63.
53. Barra S, Agostinelli S, Vagge S, et al. Radiosurgery with helical tomotherapy: Outcomes for patients with one or multifocal brain metastasis. *Technol Cancer Res Treat* 2015;14:693-699.
54. Ishihara T, Yamada K, Harada A, et al. Hypofractionated stereotactic radiotherapy for brain metastases from lung cancer: Evaluation of indications and predictors of local control. *Strahlenther Onkol* 2016;192:386-393.
55. Joshi R, Johnson MD, Maitz A, Marvin KS, Olson RE, Grills IS. Utility of graded prognostic assessment in evaluation of patients with brainstem metastases treated with radiosurgery. *Clin Neurol Neurosurg* 2016;147:30-33.
56. Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. *Ann Oncol* 2016;27:2288-2294.
57. Yomo S, Hayashi M. Is upfront stereotactic radiosurgery a rational treatment option for very elderly patients with brain metastases? A retrospective analysis of 106 consecutive patients age 80 years and older. *BMC Cancer* 2016;16:948.
58. Wolf A, Kvint S, Chachoua A, et al. Toward the complete control of brain metastases using surveillance screening and stereotactic radiosurgery. *J Neurosurg* 2018;128:23-31.
59. Mohammadi AM, Schroeder JL, Angelov L, et al. Impact of the radiosurgery prescription dose on the local control of small (2 cm or smaller) brain metastases. *J Neurosurg* 2017;126:735-743.
60. Trifiletti DM, Hill C, Cohen-Inbar O, Xu Z, Sheehan JP. Stereotactic radiosurgery for small brain metastases and implications regarding

management with systemic therapy alone. *J Neurooncol* 2017;134:289-296.
61. Murray L, Menard C, Zadeh G, et al. Radiosurgery for brainstem metastases with and without whole brain radiotherapy: Clinical series and literature review. *J Radiat Oncol* 2017;6:21-30.
62. Miller JA, Kotecha R, Ahluwalia MS, et al. Overall survival and the response to radiotherapy among molecular subtypes of breast cancer brain metastases treated with targeted therapies. *Cancer* 2017;123:2283-2293.
63. Miller JA, Kotecha R, Ahluwalia MS, et al. The impact of tumor biology on survival and response to radiation therapy among patients with non-small cell lung cancer brain metastases. *Pract Radiat Oncol* 2017;7:e263-e273.
64. Choi CYH, Wakelee HA, Neal JW, et al. Vorinostat and concurrent stereotactic radiosurgery for non-small cell lung cancer brain metastases: A phase 1 dose escalation trial. *Int J Radiat Oncol Biol Phys* 2017;99:16-21.
65. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: A single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1040-1048.
66. Koffer P, Chan J, Rava P, et al. Repeat stereotactic radiosurgery for locally recurrent brain metastases. *World Neurosurg* 2017;104:589-593.
67. Vogelbaum MA, Angelov L, Lee SY, Li L, Barnett GH, Suh JH. Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. *J Neurosurg* 2006;104:907-912.
68. Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: Results and toxicity. *Radiother Oncol* 2006;81:18-24.
69. Lutterbach J, Cyron D, Henne K, Ostertag CB. Radiosurgery followed by planned observation in patients with one to three brain metastases. *Neurosurgery* 2008;62(Suppl 2):776-784.
70. Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys* 2014;88:130-136.
71. Minniti G, Esposito V, Clarke E, et al. Fractionated stereotactic radiosurgery for patients with skull base metastases from systemic cancer involving the anterior visual pathway. *Radiat Oncol* 2014;9:110.
72. Navarria P, Pessina F, Cozzi L, et al. Hypo-fractionated stereotactic radiotherapy alone using volumetric modulated arc therapy for patients with single, large brain metastases unsuitable for surgical resection. *Radiat Oncol* 2016;11:76.
73. Narayana A, Chang J, Yenice K, et al. Hypofractionated stereotactic radiotherapy using intensity-modulated radiotherapy in patients with one or two brain metastases. *Stereotact Funct Neurosurg* 2007;85:82-87.
74. Higuchi Y, Serizawa T, Nagano O, et al. Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. *Int J Radiat Oncol Biol Phys* 2009;74:1543-1548.
75. Wang CC, Floyd SR, Chang CH, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: Efficacy and safety of an 800 cGy x 3 daily fractions regimen. *J Neurooncol* 2012;106:601-610.
76. Han JH, Kim DG, Chung HT, Paek SH, Park CK, Jung HW. Radiosurgery for large brain metastases. *Int J Radiat Oncol Biol Phys* 2012;83:113-120.
77. Wiggenraad R, Verbeek-de Kanter A, Mast M, et al. Local progression and pseudo progression after single fraction or fractionated stereotactic radiotherapy for large brain metastases. A single centre study. *Strahlenther Onkol* 2012;188:696-701.
78. Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy x 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys* 2013;86:623-629.
79. Feuvret L, Vinchon S, Martin V, et al. Stereotactic radiotherapy for large solitary brain metastases. *Cancer Radiother* 2014;18:97-106.
80. Murai T, Ogino H, Manabe Y, et al. Fractionated stereotactic radiotherapy using CyberKnife for the treatment of large brain metastases: A dose escalation study. *Clin Oncol (R Coll Radiol)* 2014;26:151-158.
81. Yomo S, Hayashi M. A minimally invasive treatment option for large metastatic brain tumors: Long-term results of two-session gamma knife stereotactic radiosurgery. *Radiat Oncol* 2014;9:132.
82. Ebner D, Rava P, Gorovets D, Cielo D, Hepel JT. Stereotactic radiosurgery for large brain metastases. *J Clin Neurosci* 2015;22:1650-1654.
83. Specht HM, Kessel KA, Oechsner M, Meyer B, Zimmer C, Combs SE. HFSRT of the resection cavity in patients with brain metastases. *Strahlenther Onkol* 2016;192:368-376.
84. Lima LC, Sharim J, Levin-Epstein R, et al. Hypofractionated stereotactic radiosurgery and radiotherapy to large resection cavity of metastatic brain tumors. *World Neurosurg* 2017;97:571-579.
85. Schultheiss TE, Orton CG, Peck RA. Models in radiotherapy: Volume effects. *Med Phys* 1983;10:410-415.
86. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665-1672.
87. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494-500.
88. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1049-1060.
89. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. *JAMA* 1998;280:1485-1489.
90. Minniti G, Scaringi C, Paolini S, et al. Single-fraction versus multifraction (3 x 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: A comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys* 2016;95:1142-1148.
91. Sneed PK, Mendez J, Vemer-van den Hoek JG, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: Incidence, time course, and factors. *J Neurosurg* 2015;123:373-386.
92. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: Proposal from the RANO group. *Lancet Oncol* 2015;16:e270-e278.