Brain metastases case series

2023

716 patients in a retrospective, single-institution cohort diagnosed with single or solitary brain metastases from 2007 to 2020. Patients receiving whole-brain radiotherapy were excluded. Cox proportional hazards models were constructed for overall survival and additional intracranial outcomes.

After adjustment for potential confounders, surgery with cavity SRT/SRS was associated with decreased all-cause mortality (hazard ratio [HR]: 0.39, 95% CI [0.27-0.57], P = 1.52 × 10-6) compared with SRT alone, along with lower risk of neurological death attributable to intracranial tumor progression (HR: 0.46, 95% CI [0.22-0.94], P = 3.32 × 10-2) and radiation necrosis (HR: 0.15, 95% CI [0.06-0.36], P = 3.28 × 10-5). Surgery with cavity SRS was also associated with decreased all-cause mortality (HR: 0.52, 95% CI [0.35-0.78], P = 1.46 × 10-3), neurological death (HR: 0.30, 95% CI [0.10-0.88], P = 2.88 × 10-2), and radiation necrosis (HR: 0.14, 95% CI [0.03-0.74], P = 2.07 × 10-2) compared with SRS alone. Surgery was associated with lower risk of all-cause mortality and neurological death in cardinality-matched subsets of the cohort. Among surgical patients, gross total resection was associated with extended overall survival (HR: 0.62, 95% CI [0.40-0.98], P = 4.02 × 10-2) along with lower risk of neurological death (HR: 0.31, 95% CI [0.17-0.57], P = 1.84 × 10-4) and local failure (HR: 0.34, 95% CI [0.16-0.75], P = 7.08 × 10-3).

In patients with 1 brain metastasis, minimizing intracranial disease specifically before stereotactic radiation is associated with improved oncologic outcomes [1)]

Twenty-nine patients with systemic cancer and brain metastases (≥ 2.7 cm in greatest diameter) who underwent single-session SRS were included.

Among 29 patients, 69% of patients had either lung cancer, melanoma, or breast cancer. The median initial tumor size (maximal diameter) was 32 mm (range 28-43), and the median initial tumor volume was 9.56 cm3 (range 1.56-25.31). The median margin dose was 16 Gy (range 12-18). The average percent decrease in tumor volume compared to pre-SRS volume was 55% on imaging at 1-2 months, 58% at 3-5 months, 64% at 6-8 months, and 57% at > 8 months. There were no adverse events immediately following SRS. Median corticosteroid use after SRS was 21 days. Median survival after radiosurgery was 15 months.

Initial high-dose corticosteroid therapy followed by prompt single-stage SRS is a safe and efficacious method to manage patients with LBMs (defined as ≥ 2.7 cm) [2)].

Between 2010 and 2020, data from 184 patients treated for 915 brain metastases via two to six stereotactic radiotherapy sessions for local or distant BM recurrence without previous or intercurrent WBRT were retrospectively reviewed. Patients were seen via consultations during SRT, and the delivered dose, the use of corticosteroid therapy and neurological symptoms were recorded and rated according to the Common Terminology Criteria for Adverse Events CTCAEv4. The dosimetric characteristics of 79% of BMs were collected, and summation plans of 76.6% of BMs were created.

36% of patients developed acute toxicity during at least one session. No grade three or four toxicity was registered, and grade one or two cephalalgy was the most frequently reported symptom. There was no significant difference in the occurrence of acute toxicity between consecutive SRT sessions. In the multivariate analysis, acute toxicity was associated with the use of corticosteroid therapy before irradiation (OR = 2.6; p = 0.01), BMV grade (high vs. low grade OR = 5.17; p = 0.02), and number of SRT sessions (3 SRT vs. 2 SRT: OR = 2.64; p = 0.01). The median volume equivalent to the WBRT dose (VWBRT) was 47.9 ml. In the multivariate analysis, the VWBRT was significantly associated with the total GTV ($p < 0.001$) and number of BMs ($p < 0.001$). Even for patients treated for more than ten cumulated BMs, the median BED to the brain was very low compared to the dose delivered during WBRT.

Repeated SRT for local or distant recurrent BM is well tolerated, without grade three or four toxicity, and does not cause more acute neurological toxicity with repeated SRT sessions. Moreover, even for patients treated for more than ten BMs, the VWBRT is low [3].

2021

1132 patients with BMs in their institutional registry. Ninety-five patients were treated for ≥ 25 cumulative metastases, resulting in a total of 3596 tumors treated during 373 separate treatment sessions. The median number of SRS sessions per patient was 3 (range 1-12 SRS sessions), with nearly all patients (n = 93, 98%) having > 1 session. On univariate analysis, factors affecting OS in a statistically significant manner included histology, tumor volume, tumor number, diagnosis-specific graded prognostic assessment (DS-GPA), brain metastases velocity (BMV), and need for subsequent whole-brain radiation therapy (WBRT). The median of the mean WB dose was 4.07 Gy (range 1.39-10.15 Gy). In the top quartile for both the highest cumulative number and highest cumulative volume of treated metastases, the median of the mean WB dose was 6.14 Gy (range 4.02-10.15 Gy). Seventy-nine patients (83%) had all treated tumors controlled at last follow-up, reflecting the high and durable control rate. Corticosteroids for tumor- or treatment-related effects were prescribed in just over one-quarter of the patients. Of the patients with radiographically proven adverse radiation effects (AREs; 15%), 4 were symptomatic. Four patients required subsequent craniotomy for hemorrhage, progression, or AREs.

In selected patients with a large number of cumulative BMs, multiple courses of SRS are feasible and safe. Together with new systemic therapies, the study results demonstrate that the achieved survival rates compare favorably to those of larger contemporary cohorts, while avoiding WBRT in the majority of patients. Therefore, along with the findings of other series, this study supports SRS as a standard practice in selected patients with larger numbers of BMs [4].

2020

Lee et al. retrospectively analyzed data for 311 patients treated with Gamma Knife radiosurgery at a single institute. The mean age at time of treatment was 60 years (range 23-86 years), and the median Karnofsky performance status (KPS) score was 90 (range 60-100). Using a new prognostic index, the prognostic index for brain metastases (PIBM), the patients were categorized into 3 groups according to the primary tumor status and KPS score. We performed survival analysis and compared the prognostic ability of the PIBM with other published indices.

During the median follow-up duration of 8.2 months (range 0.1-109 months), the median overall

survival rate was 9.1 months. Stable primary tumor status (hazard ratio [HR] 0.497, 95% confidence interval [CI] 0.321-0.769, p = 0.002) and KPS score ≥90 (HR 1.407, 95% CI 1.018-1.946, p = 0.039) significantly predicted longer overall survival. The PIBM showed the lowest Akaike information criterion value and the highest integrated area under the curve value compared with other prognostic indices.

The PIBM may be a more accurate prognostic indicator than other published indices. Although this new and practical prognostic index requires further validation in larger cohort studies, they suggested that the PIBM could be useful to predict survival rate and inform appropriate management of patients with brain metastases [5)]

2019

A retrospective study with consecutive patients with brain metastases treated with LITT. Based on radiological aspects, lesions were divided into progressive disease after SRS (recurrence or radiation necrosis) and new lesions. The primary endpoint was time to local recurrence.

A total of 61 consecutive patients with 82 lesions (5 newly diagnosed, 46 recurrences, and 31 radiation necrosis). Freedom from local recurrence at 6 mo was 69.6%, 59.4% at 12, and 54.7% at 18 and 24 mo. Incompletely ablated lesions had a shorter median time for local recurrence (P < .001). Larger lesions (>6 cc) had shorter time for local recurrence (P = .03). Dural-based lesions showed a shorter time to local recurrence (P = .01). Tumor recurrence/newly diagnosed had a shorter time to local recurrence when compared to RN lesions (P = .01). Patients receiving systemic therapy after LITT had a longer time to local recurrence (P = .01). In multivariate Cox-regression model, the HR for incomplete ablated lesions was 4.88 (P < .001), 3.12 (P = .03) for recurrent tumors, and 2.56 (P = .02) for patients not receiving systemic therapy after LITT. The complication rate was 26.2%.

Incompletely ablated and recurrent tumoral lesions were associated with a higher risk of treatment failure and were the major predicting factors for local recurrence. Systemic therapy after LITT was a protective factor regarding local recurrence [6)].

Wolpert et al. identified 799 patients diagnosed with Brain metastases (BM) by retrospective screening there electronic chart system. Candidate risk factors for the development of epilepsy were tested by univariate and multivariate Cox regression models.

Epilepsy was diagnosed in 226 of 799 patients (28%). Risk factors for epilepsy in non-operated patients were single BM (p=0.002, hazard ratio (HR) 3.2, 95% confidence interval (CI) 1.5-6.6) and detection of tumoral hemorrhage (p= 0.008, HR 2.5, 95% CI 1.3-4.9). Pre-operative seizures occurred predominantly in patients with supratentorial BM (p=0.003, HR 20.78, 95% CI 2.8-153.4) and lung cancer (p= 0.022; HR 2.0, 95% CI 1.1-3.6). Post-operative seizures were associated with supratentorial localization (p=0.017, HR 5.8, 95% CI 1.4-24.3), incomplete resection (p=0.005, HR 4.6, 95% CI 1.6-13.1), and by trend for multiple brain surgeries (p=0.095, HR 1.9, 95%CI 0.9-4.0). These risk factors were integrated into a predictive score model for post-operative epilepsy (score sum 0-8). A gradual increase of seizure rates along with higher sum score was confirmed post-hoc (score 0, no seizures; score 8, 48% seizures). Receiver-operating characteristic analysis supported diagnostic accuracy (p=0.00001, AUC=0.75).

Wolpert et al. defined risk profiles for the development of BM-related epilepsy and derived a score

which might help to estimate the risk of post-operative seizures and identify individuals at risk who might benefit from primary prophylactic antiepileptic drug therapy [7].

Patients diagnosed with limited brain metastases (LBM) were entered into a database between January 2010 and February 2017. Patients were recommended WBRT avoidance with focal radiation therapy and three-monthly magnetic resonance imaging. The primary endpoint was overall survival. Secondary endpoints included progression free survival, initial-site failure (ISF), distant brain relapse (DBF), leptomeningeal disease and rate of WBRT. Analysis involved Kaplan Meier survival estimate with log-rank tests and Cox regression analysis.

One hundred and sixty-six patients were managed with median follow-up of 13 months and median overall survival of 15 months (95% confidence interval (CI) 10.8-19.2). Eighty-three patients had central nervous system (CNS) relapse with median progression free survival of 11 months (95% CI 6.7-15.3), of which most failures were DBF (83.1%) with 27 ISF (32.5%). Of the ISFs, 12 (43%) had surgery alone, six had chemotherapy alone and nine received RT. Surgery or chemotherapy alone compared with RT had a significantly higher incidence of ISF with a hazard ratio of 4.96 ($P < 0.0001$, 95% CI 2.10-11.83) and 6.54 ($P = 0.001$, 95% CI 2.26-18.87), respectively. WBRT was utilized in only 24 patients, with 83% patients free of WBRT at 12 months. On univariate analysis, number of metastases ($P = 0.04$), symptomatic extracranial disease ($P = 0.04$) and early CNS relapse within 6 months ($P < 0.01$) had worse survival. No grade 3-4 toxicity events were noted in 129 patients undergoing RT [8]

2018

An institutional review board-approved, retrospective cohort study using a prospectively accumulated database including 833 patients (patients with whole brain radiotherapy were excluded) who underwent a second SRS procedure for newly-detected lesions using a gamma knife for BMs during the 19-year-period between July, 1998 and June, 2017. Furthermore, among these 833 patients, 250 underwent a third and 88 a fourth SRS procedure.

The median survival times (MSTs, months) after the second SRS were 12.9 (95% CI; 10.2-17.1), 7.5 (6.5-9.0) and 5.1 (4.0-5.6) in the BMV ≤3, 4-13 and ≥14 groups (p=0.0001). The corresponding MSTs after the third SRS were 13.2 (95% CI; 9.1-21.6), 8.0 (6.2-11.2) and 5.7 (4.8-7.8). (p=0.0001). Respective MSTs after the fourth SRS were 13.2 (95% CI; 9.1-21.6), 8.0 (6.2-11.2) and 5.7 (4.8-7.8) (p<0.0001). The mean BMV score of small cell lung cancer patients, 24.8, was significantly higher than that of non-small cell lung cancer patients, 17.7 (p=0.032).

The present results support the validity of brain metastases velocity (BMV) for predicting survival not only after the second but also the third and fourth SRS [9].

At the Toronto Western Hospital they have historically treated Brain metastases (BM) ≤ 2cm in eloquent brain with a radiosurgery (SRS) lower prescription dose (PD) to reduce the risk of radionecrosis (RN). They sought to evaluate the impact of this practice on outcomes and analyzed a prospective registry of BM patients treated with SRS between 2008 and 2017. Incidences of local failure (LF) and RN were determined and Cox regression was performed for univariate and

multivariable analyses (MVA).

1,533 BM ≤2cm were evaluated. Median radiographic follow-up post SRS was 12.7 months (1.4-100). Overall, the 2year incidence of LF was lower for BM treated with PD≥21Gy (9.3%) compared with PD≤15Gy (19.5%);(subHR 2.3; 95CI 1.4-3.7;p=0.0006). The 2-year incidence of RN was not significantly higher for the group treated with PD ≥21Gy (9.5%) compared to the PD ≤15Gy group (7.5%) (p=0.16). MVA demonstrated that PD (≤15 Gy) and tumor size (>1cm) were significantly correlated (p<0.05) with higher rates of LF, and RN, respectively. For tumors ≤1 cm, when comparing PD ≤15Gy to ≥21Gy, the risks of LF and RN are equivalent. However, for lesions >1cm, PD ≥21Gy is associated with a lower incidence of LF without significantly increasing the risk of RN.

The results indicate that rates of LF or RN following SRS for BM are strongly correlated to size and PD. Based on this results, they now, depending upon the clinical context, consider increasing PD to 21 Gy for BM in eloquent brain, excluding the brain stem [10].

Berger et al., from Tel Aviv, Israel, conducted a prospective single arm cohort study of patients with 1-2 Brain metastases (BM), who underwent resection of a single BM between May 2015 to December 2016. Patients were evaluated for cognitive functions (NeuroTrax computerized neuropsychological battery; Modiin, Israel) and quality of life (QOL; QLQ-30, QLQ-BN20) before and 3 months following post-resection SRS.

Twelve out of 14 patients completed pre- and post-SRS neurocognitive assessments. Overall, they did not detect significant neurocognitive or QOL changes 3 months following SRS. In a subgroup analysis among patients younger than 60 years, median global cognitive score increased from a pre-treatment score of 88 (72-102) to 95 (79-108), 3 months following SRS treatment, p = 0.042; Wilcoxon signed rank test. Immediate verbal memory and executive functions scores increased from 86 (72-98) to 98 (92-112) and 86 (60-101) to 100 (80-126), respectively, p = 0.043. No significant cognitive changes were discovered among patients at the age of 60 or older.

Post-resection radiosurgery has a safe neuro-cognitive profile and is associated with preservation of nearly all quality of life parameters. Patients younger than 60 years benefit most and may even regain some cognitive functions within a few months after treatment [11].

Balermpas et al., retrospectively evaluated patients with brain metastases treated with re-SRS for local tumor progression between 2011 and 2017. Patient and treatment characteristics as well as rates of tumor control, survival and toxicity were analyzed.

Overall, 32 locally recurrent brain metastases in 31 patients were irradiated with re-SRS. Median age at re-SRS was 64.9 years. The primary histology was breast cancer and non-small-cellular lung cancer (NSCLC) in respectively 10 cases (31.3%), in 5 cases malignant melanoma (15.6%). In the first SRS-course 19 metastases (59.4%) and in the re-SRS-course 29 metastases (90.6%) were treated with CyberKnife® and the others with Gamma Knife. Median planning target volume (PTV) for re-SRS was 2.5 cm3 (range, 0.1-37.5 cm3) and median dose prescribed to the PTV was 19 Gy (range, 12-28 Gy) in 1-5 fractions to the median 69% isodose (range, 53-80%). The 1-year overall survival rate was 61.7% and the 1-year local control rate was 79.5%. The overall rate of radiological radio-necrosis was 16.1% and four patients (12.9%) experienced grade ≥ 3 toxicities.

A second course of SRS for locally recurrent brain metastases after prior local SRS appears to be

feasible with acceptable toxicity and can be considered as salvage treatment option for selected patients with high performance status. Furthermore, this is the first study utilizing robotic radiosurgery for this indication, as an additional option for frameless fractionated treatment [12].

The purpose of a study was to determine if there is a threshold tumor size below which local control (LC) rates approach 100%, and to relate these findings to the use of routine surveillance brain imaging. METHODS From a prospective registry, 200 patients with 1237 brain metastases were identified who underwent SRS between December 2012 and May 2015. The median imaging follow-up duration was 7.9 months, and the median margin dose was 18 Gy. The maximal diameter and volume of tumors were measured. Histological analysis included 96 patients with non-small cell lung cancers (NSCLCs), 40 with melanoma, 35 with breast cancer, and 29 with other histologies. RESULTS Almost 50% of brain metastases were NSCLCs and commonly measured less than 6 mm in maximal diameter or 70 mm3 in volume. Thirty-three of 1237 tumors had local progression at a median of 8.8 months. The 1- and 2-year actuarial LC rates were 97% and 93%, respectively. LC of 100% was achieved for all intracranial metastases less than 100 mm3 in volume or 6 mm in diameter. Patients whose tumors at first SRS were less than 10 mm maximal diameter or a volume of 250 mm3 had improved overall survival. CONCLUSIONS SRS can achieve LC rates approaching 100% for subcentimeter metastases. The earlier initial detection and prompt treatment of small intracranial metastases may prevent the development of neurological symptoms and the need for resection, and improve overall survival. To identify tumors when they are small, routine surveillance brain imaging should be considered as part of the standard of care for lung, breast, and melanoma metastases. ■ CLASSIFICATION OF EVIDENCE Type of question: prognostic; study design: retrospective cohort; evidence: Class II [13].

2017

Between July 2000 and July 2017, 377 patients with brain metastases were treated with upfront SRS. We performed a large, single institution retrospective analysis of these patients. Kaplan Meier analysis was used to estimate survival times. Competing risk analysis was used to estimate times to local failure (LF) and distant brain failure (DBF). Multivariate analysis was performed to estimate the hazard ratios (HRs) for overall survival (OS), neurologic and non-neurologic death for patients with 1, 2 and 3+ lines of prior systemic therapy.

RESULTS: Of the 1077 patients with brain metastases treated with SRS, 377 received prior systemic therapy with a median of 1 (range: 1-9) lines of prior therapy. Median OS was 8.70 months (95% CI, 7.9-9.5). Median OS for patients with 1 prior line of therapy, 2 prior lines of therapy and 3 or greater lines of therapy were 9.93-, 9.05-, and 6.18-months, respectively (log rank p = .04). Lines of therapy as a continuous variable was not associated with LF or DBF on competing risk analysis. The percentage of patients that died of neurological death was 36%. Greater prior lines of therapy (1 vs. 2 vs. 3 and greater) was associated with a greater likelihood of dying of non-neurologic death (gray's p = .01), but was not associated with likelihood of dying of neurologic death (p = .57).

Lines of therapy are associated with OS and non-neurologic death but are not associated with neurologic death, LF or DBF [14].

A total of 79 resected lesions from 73 patients were evaluated. An Receiver operating characteristic (ROC) curve of local failure (LF) and time to initiation (TTI) identified an optimal threshold for TTI of

30.5 days, with an area under the curve of 0.637. TTI > 30 days was associated with an increased hazard of LF (HR 4.525, CI 1.239-16.527) but was not significantly associated with survival (HR 1.002, CI 0.547-1.823) or distant brain failure (DBF, HR 1.943, CI 0.989-3.816). Fifteen patients (20.5%) required post-operative inpatient rehabilitation. Post-operative rehabilitation was associated with TTI > 30 days (OR 1.48, CI 1.142-1.922). In the study of resected brain metastases, longer time to initiation of post-operative radiosurgery was associated with increased local failure. Ideally, post-op SRS should be initiated within 30 days of resection if feasible [15].

A retrospective review was performed of 59 patients with brain metastases who underwent ≥3 SRS courses for new lesions. Cox regression analyzed factors predictive for overall survival.

The median age at diagnosis was 52 years. Over time, patients underwent a median of 3 courses of SRS (range: 3-8) to a total of 765 different brain metastases. The 6-month risk of distant intracranial recurrence after the first SRS treatment was 64% (95% confidence interval: 52%-77%). Overall survival was 40% (95% confidence interval: 28%-53%) at 24 months. Only 24 patients (41%) had a decline in their Karnofsky Performance Status ≤70 at last office visit. Quality of life was preserved among 77% of patients at 12 months, with 45% experiencing clinically significant improvement during clinical follow-up. Radiation necrosis developed in 10 patients (17%). On multivariate analysis, gender (males, Hazard Ratio [HR]: 2.0, P < .05), Karnofsky Performance Status ≤80 (HR 3.2, P < .001), extracranial metastases (HR: 3.6, P < .001), and a distant intracranial recurrence ≤3 months from initial to repeat SRS (HR: 3.8, P < .001) were associated with a poorer survival.

In selected patients, performing ≥3 SRS courses controls intracranial disease. Patients may need salvage SRS for distant intracranial relapse, but focal retreatments are associated with modest toxicity, do not appear to negatively affect a patient's performance status, and help preserve quality of life [16].

Patients with brain metastases diagnosed between 2003-2015 who underwent repeat SRS for local tumor progression following prior SRS were identified. Rates of local control, radiation necrosis, and overall survival were analyzed. Factors affecting local failure and radiation necrosis were assessed by Chi-squared test. RESULTS: 24 lesions in 22 patients underwent repeat SRS in a single fraction. Median age was 59 years. The median SRS-1 dose was 18 Gy and the median SRS-2 dose was 15.5 Gy. The median SRS-1 target volume was 2.25 cm3 and the median SRS-2 target volume was 3.30 cm3. The median follow up from SRS-2 was 8.8 months. The actuarial local control for SRS-2 was 94.1% and 61.1% at 6 and 12 months, respectively. Actuarial radiation necrosis was 9.2% and 9.2% at 6 and 12 months, respectively. Volume of tumor >4 cm3 correlated with increased risk of local failure (p=0.006) with no local failures recorded with volumes ≤4 cm3. SRS-2 dose, cumulative SRS dose, receipt of WBRT, and use of SRS-2 as boost after surgery did not correlate with local failure or radiation necrosis. Median overall survival after SRS-2 was 8.78 months. CONCLUSION: Repeat SRS is feasible for select patients particularly for those with tumor volume ≤4 cm3. Further evaluation is needed to establish the most appropriate treatment doses and volumes for this approach [17].

A study reviewed patients receiving SRS for BM between 2008-2012 who underwent a biopsy for suspicion of RN versus LR on MRI imaging. Data collection included: demographics, radiation parameters, imaging findings, post-biopsy pathology. Kaplan-Meier methods determined overall

survival (OS). Fisher's exact test assessed for association between lesion biopsy result and variables of interest.

Thirty-four patients with 35 biopsied BM were included. Lesions were biopsied a median of 8.8 months after SRS. Most patients had primary lung cancer (11; 31.4%). Eleven (31.4%) biopsies were positive for LR and 24 (68.6%) showed RN only. Median OS was longer for patients with RN (31.0 months) than for patients with LR (14.5 months; p = 0.135). Time from SRS to biopsy was significantly different between RN and LR groups; 10 lesions (52.5%) biopsied ≤9 months after SRS showed LR, whereas 1 lesion (6.3%) biopsied >9 months after SRS showed LR (p = 0.004). For 16 (65.7%) lesions, management was changed or directed by the biopsy results.

Stereotactic biopsy for accessible enlarging lesions after SRS appears diagnostically valuable in patients with few lesions and changes clinical management. RN should be suspected in patients with an enlarging lesion more than 9 months post-SRS [18].

2016

Between 2002 and 2015, 32 patients were treated with repeat SRS for local recurrence of ≥ 1 brain metastases following initial SRS treatment. The Kaplan-Meier method was used to estimate time-to-event outcomes including overall survival (OS), local failure, and radiation necrosis. Cox proportional hazards analysis was performed for predictor variables of interest for each outcome. Composite dose-volume histograms were constructed for each reirradiated lesion, and these were then used to develop a predictive dosimetric model for radiation necrosis. RESULTS Forty-six lesions in 32 patients were re-treated with a second course of SRS after local failure. A median dose of 20 Gy (range 14-22 Gy) was delivered to the tumor margin at the time of repeat SRS. Local control at 1 year was 79% (95% CI 67%-94%). Estimated 1-year OS was 70% (95% CI 55%-88%). Twelve patients had died at the most recent follow-up, with 8/12 patients experiencing neurological death (as described in Patchell et al.). Eleven of 46 (24%) lesions in 11 separate patients treated with repeat SRS were associated with symptomatic radiation necrosis. Freedom from radiation necrosis at 1 year was 71% (95% CI 57%-88%). Analysis of dosimetric data revealed that the volume of a lesion receiving 40 Gy (V40Gy) was the most predictive factor for the development of radiation necrosis (p = 0.003). The following V40Gy thresholds were associated with 10%, 20%, and 50% probabilities of radiation necrosis, respectively: 0.28 cm3 (95% CI 3%-28%), 0.76 cm3 (95% CI 9%-39%), 1.60 cm3 (95% CI 26%-74%). CONCLUSIONS Repeat SRS appears to be an effective salvage option for patients with brain metastases experiencing local failure following initial SRS treatment. This series demonstrates durable local control and, although rates of radiation necrosis are significant, repeat SRS may be indicated for select cases of local disease recurrence. Because the V40Gy is predictive of radiation necrosis, limiting this value during treatment planning may allow for a reduction in radiation necrosis rates [19].

A total of 294 patients underwent SRS to 697 lesions, of which 65 patients had controlled systemic disease (CSD). Median follow-up was 9.7 mos. There was no difference in local control between the two cohorts (p=0.795). Regional CNS control was significantly better for patients with CSD, 68% vs. 48% (p=0.001). Overall survival at 1 and 5 years for CSD were 65% and 13%, with USD yielding 41% and 7% (p<0.001). Multivariate analysis demonstrated that USD (relative CSD) independently predicts regional failure (HR1.75; p=0.008) and shorter overall survival (HR1.55; p=0.007).

Patients presenting with brain metastases after ≥1 year of primary and systemic disease control

represent a particularly favorable cohort, with lower regional CNS failure and prolonged survival, for an approach of SRS alone [20].

2015

All cases of brain metastases treated from 1998 through 2009 with Gamma Knife SRS at UCSF were considered. Cases with less than 3 months of follow-up imaging, a gap of more than 8 months in imaging during the 1st year, or inadequate imaging availability were excluded. Brain scans and pathology reports were reviewed to ensure consistent scoring of dates of ARE, treatment failure, or both; in case of uncertainty, the cause of lesion worsening was scored as indeterminate. Cumulative incidence of ARE and failure were estimated with the Kaplan-Meier method with censoring at last imaging. Univariate and multivariate Cox proportional hazards analyses were performed. RESULTS: Among 435 patients and 2200 brain metastases evaluable, the median patient survival time was 17.4 months and the median lesion imaging follow-up was 9.9 months. Calculated on the basis of 2200 evaluable lesions, the rates of treatment failure, ARE, concurrent failure and ARE, and lesion worsening with indeterminate cause were 9.2%, 5.4%, 1.4%, and 4.1%, respectively. Among 118 cases of ARE, approximately 60% were symptomatic and 85% occurred 3-18 months after SRS (median 7.2 months). For 99 ARE cases managed without surgery or bevacizumab, the probabilities of improvement observed on imaging were 40%, 57%, and 76% at 6, 12, and 18 months after onset of ARE. The most important risk factors for ARE included prior SRS to the same lesion (with 20% 1-year risk of symptomatic ARE vs 3%, 4%, and 8% for no prior treatment, prior whole brain radiotherapy [WBRT], or concurrent WBRT) and any of these volume parameters: target, prescription isodose, 12-Gy, or 10-Gy volume. Excluding lesions treated with repeat SRS, the 1-year probabilities of ARE were < 1%, 1%, 3%, 10%, and 14% for maximum diameter 0.3-0.6 cm, 0.7-1.0 cm, 1.1-1.5 cm, 1.6-2.0 cm, and 2.1-5.1 cm, respectively. The 1-year probabilities of symptomatic ARE leveled off at 13%-14% for brain metastases maximum diameter > 2.1 cm, target volume > 1.2 cm(3), prescription isodose volume > 1.8 cm(3), 12-Gy volume > 3.3 cm(3), and 10-Gy volume > 4.3 cm(3), excluding lesions treated with repeat SRS. On both univariate and multivariate analysis, capecitabine, but not other systemic therapy within 1 month of SRS, appeared to increase ARE risk. For the multivariate analysis considering only metastases with target volume > 1.0 cm(3), risk factors for ARE included prior SRS, kidney primary tumor, connective tissue disorder, and capecitabine. CONCLUSIONS: Although incidence of ARE after SRS was low overall, risk increased rapidly with size and volume, leveling off at a 1-year cumulative incidence of 13%-14%. This study describes the time course of ARE and provides risk estimates by various lesion characteristics and treatment parameters to aid in decision-making and patient counseling [21].

2014

Effectiveness of Gamma Knife radiosurgery (GKRS: Elekta AB, Stockholm, Sweden) for patients with metastatic brain disease and the prognostic factors influencing their survival were analyzed in a 5year retrospective data analysis (July 2001 to June 2006). Kaplan-Meier survival curves were constructed using univariate and multivariate analyses with the respective salient prognostic factors. This study analyzed data on 330 patients with brain metastases who underwent GKRS. Lung carcinoma (55%) was the most common primary cancer followed by breast (17.8%), melanoma (9.4%), colorectal (4.8%) and renal (3.9%). The median survival for all patients was 8months. Survival ranged from 13months for breast metastases, 10months for renal, and 8months for lung to 5months for colorectal and melanoma. Mean age of patients was 58.5years (range 18-81). Melanoma patients were younger with a mean age of 49 and also had the highest number of lesions (3.8) when compared to patients

with renal (2.5), lung (2.8), colorectal (3) and breast (3.6). When stratified according to the number of lesions patient survival was 8months (one to three lesions), 7.5months (four or five lesions) and 7months (six lesions or more). Mean Karnofsky Performance Status score (KPS) was 77 and survival dropped significantly from 8months to 4.5months if KPS was less than 70. Survival improved with a KPS of 70 or more, regardless of the number of lesions treated. Selection of patients based on the number of lesions may not be justified. A prospective trial is required to further define the prognostic factors affecting survival [22].

1)
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