Resecting the Dominant Lesion: Patient Outcomes after Surgery and Radiosurgery vs Stand-Alone Radiosurgery in the Setting of Multiple Brain Metastases

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Abstract

BACKGROUND: Brain metastases are the most common central nervous system (CNS) tumors, occurring in 300,000 people per year in the US. The benefit of surgical resection, over radiosurgery, for dominant lesions remains unclear.

METHODS: The University of Pennsylvania Health System database was retrospectively reviewed for patients presenting with multiple brain metastases from 1/1/16 to 8/31/18 with one dominant lesion > 2 cm in diameter, who underwent initial treatment with either resection of the dominant lesion or Gamma Knife radiosurgery (GKS). Inclusion criteria were age ≥ 18, >1 brain metastasis, and presence of a dominant lesion (>2 cm). We analyzed factors associated with mortality.

RESULTS: 129 patients were identified (surgery=84, GKS=45). The median number of intracranial metastases was 3 (IQR: 2-5). The median diameter of the largest lesion was 31 mm (IQR: 25-38) in the surgery group vs 21 mm (IQR: 20-24) in the GKS group (p<0.001). Mortality did not differ between surgery and GKS patients (69.1% vs 77.8%, p = 0.292). In a multivariate survival analysis, there was no difference in mortality between the surgery and GKS cohorts (aHR: 1.35, 95% CI: 0.74-2.45 p=0.32). Pre-operative KPS (aHR: 0.97, 95% CI: 0.95-0.99, p=0.004), CNS radiotherapy (aHR: 0.33, 95% CI: 0.19-0.56 p<0.001), chemotherapy (aHR: 0.27, 95% CI: 0.15-0.47, p<0.001), and immunotherapy (aHR: 0.41, 95% CI: 0.25-0.68, p=0.001) were associated with decreased mortality.

CONCLUSION: In our institution, patients with multiple brain metastases and one symptomatic dominant lesion demonstrated similar survival after GKS when compared with up-front surgical resection of the dominant lesion.

Introduction

Brain metastases are the most common central nervous system (CNS) tumors, occurring in 300,000 people per year in the US, far outnumbering cases of primary brain tumors. Approximately 1.7 million people are diagnosed with cancer annually, and of these patients, up to 40% go on to develop one or more intracranial metastases [1–3]. Moreover, incidence of metastatic brain cancer is increasing due to improved diagnostic testing and systemic therapies that have afforded cancer patients longer survival [4]. Among the most common cancers to metastasize to the brain are lung, breast, melanoma, and genitourinary tract cancers [5]. Only 10-20% of brain metastases present as solitary tumors; the vast majority occur as multiple metastases [6].

Historically, due to inadequate control of systemic disease as well as poor performance status, patients with multiple brain metastases had limited life expectancy, and whole brain radiotherapy (WBRT) with corticosteroids remained standard of care [7–10]. This has changed over the past few decades. Advances in neurosurgical techniques, improved surveillance, more effective systemic therapies, and the advent of stereotactic radiosurgery (SRS) have broadened the therapeutic options for patients with
multiple metastases [11]. There is evidence in support of both SRS and surgical resection in the treatment of solitary brain metastases, with similar reported rates of overall survival [5, 9, 10, 12–16].

Indications for surgery for multiple, synchronous metastases remain highly debated. Traditionally, surgical resection is reserved for patients with better performance status, stable systemic disease, and symptomatic mass effect from a dominant lesion, with adjuvant SRS to the operative bed and additional smaller metastases [2, 8, 17, 18]. Recent evidence has demonstrated the efficacy of SRS without upfront surgery for improving both tumor control and survival in the setting of multiple metastases, but direct comparisons with conventional surgical resection are few in number [19–23]. A limited number of retrospective reviews have reported survival benefit after resection of multiple metastases, but there is a great need for higher-quality evidence reflecting contemporary practice patterns [5, 18, 24, 25].

Given the conflicting evidence, we analyzed factors associated with mortality in patients with multiple intracranial metastases with one dominant lesion undergoing surgery followed by SRS or standalone SRS [2, 18].

Methods

UPHS Protocol for Management of Multiple Intracranial Metastases

Within University of Pennsylvania Health System (UPHS), patients who present with multiple metastases, and at least one dominant lesion (>=2 cm in diameter) causing profound vasogenic edema and neurologic deficits, are offered surgical intervention upfront. Patients with a dominant lesion, but without profound symptoms, are offered SRS using Gamma Knife radiosurgery (GKS) to all lesions. Nearly all patients who undergo surgical resection undergo GKS to the tumor bed as well as unresected metastases 4-6 weeks after surgical resection. Occasionally, those with poor functional status and/or leptomeningeal disease are offered WBRT, while a select few undergo CyberKnife (CK). For the purposes of our manuscript, both patients who underwent radiotherapy after surgical resection and those who underwent additional radiotherapy after upfront GKS, were categorized as having undergone “adjuvant or repeat radiotherapy”. Those who required either additional surgery after primary resection or after upfront GKS, were categorized as receiving “adjuvant or repeat surgery”.

Patient Selection

The UPHS database was queried for patients presenting with multiple brain metastases from 1/1/16 to 8/31/18, and who underwent up-front resection of a symptomatic dominant lesion vs Gamma Knife radiosurgery (GKS). Inclusion criteria was age ≥ 18, presence of >1 brain metastasis, and a dominant lesion ≥ 2 cm in diameter. Patients with prior craniotomies, WBRT, or GKS were excluded. We analyzed factors associated with survival.

Data Collection
The Department of Neurosurgery oncology databases were queried for patients who underwent craniotomy for tumor within UPHS from January 1, 2016 to August 31, 2018, using the following Current Procedural Terminology (CPT) codes: 61500, 61510, 61518. 1516 patients were identified using the above CPT codes. The electronic medical records were reviewed to exclude patients that underwent craniotomies for indications other than brain tumors. The remaining 965 patients were reviewed to exclude those with diagnoses of primary brain tumor, including glioma and meningioma. The remaining 365 patients were screened for those presenting with solitary metastasis on pre-operative imaging. 149 patients were identified who underwent craniotomy in the setting of two or more brain metastases. After excluding patients whose dominant lesions were <2 cm in largest dimension, 101 total patients met our inclusion criteria prior to neurosurgical intervention in the specified timeframe. 84 of these had complete information and follow up upon review of the medical record. Figure 1 contains a flow diagram for inclusion within the patient cohort.

The Department of Neurosurgery Gamma Knife database was queried for patients who presented within the same time frame with a diagnosis of multiple brain metastases, who underwent solely Gamma Knife treatment. Any patients who had undergone prior up-front surgical resection were excluded. Imaging was reviewed to confirm the presence of a “dominant lesion”, defined as 2 cm or greater, to best match the primary cohort of interest. 45 total patients were identified.

Variables of interest were reviewed and collected into a password protected database using Excel V16.25 (Microsoft, 2019).

Data Analysis

Data was analyzed in Stata 12.1 (StataCorp LLC, College Station, Texas, USA). Demographic, clinical characteristics, and outcomes of patients were analyzed using descriptive statistics. Differences in the demographics, clinical characteristics and outcomes of interest between the two patient cohorts (GKS vs surgery) were determined using Mann-Whitney U test for continuous variables and \( \chi^2 \) test for categorical variables. Cox proportional hazards regression model was then used to perform a survival analysis to assess association between variables of interest and overall survival, taking into account possible confounders. The proportional hazards assumption was checked to ensure model accuracy using Schoenfeld residuals. Kaplan-Meier survival curves were used to further analyze post-intervention survival in patients undergoing GKS vs surgery, those receiving adjuvant CNS radiotherapy post primary intervention and those receiving adjuvant chemotherapy. Sensitivity analysis was performed, excluding patients in whom the largest metastasis was >3.5cm and >3.0cm from the cohort. Statistical significance was defined as \( p < 0.05 \).

Ethical Considerations

All patient information was de-identified and information was stored in a password protected database. All research was conducted in accordance with the standards of the University of Pennsylvania Institutional Review Board.
Results

Demographics & Clinical Characteristics

129 patients were identified (surgery=84, GKS=45). Median age was 60 year (IQR: 52-67)), and 52.7% were female. The most common primary cancer was lung (48.1%). The median number of metastases was 3 (IQR: 2-5), and the median diameter of the largest lesion was 26 mm (IQR: 21-35). In 73.6% of patients the largest metastasis was supratentorial. The median pre-intervention Karnofsky Performance Status (KPS) score was 80 (IQR: 70-90). Among all patients, most were classified into recursive partitioning analysis (RPA) class II (52.7%). There was no statistically significant difference in demographics, total number of CNS metastases, location of metastases, pre-intervention KPS scores and RPA class between surgery and GKS cohorts (Table 1). The median diameter of the largest metastasis was slightly larger for the surgery cohort compared to GKS, 31 mm (IQR 25-38) vs 21 (IQR: 20-24), respectively (p<0.001) (Table 1). Patients within the surgery cohort underwent adjuvant or repeat CNS radiotherapy more frequently than those within the GKS cohort (78.6% vs 40.0%, respectively; p<0.001). There was other difference between surgery and GKS cohorts in the adjuvant treatments received (additional surgery, chemotherapy or immunotherapy).

Outcomes

The median follow up period was 23 months (IQR: 10-50). The median change in KPS pre and post-intervention was -10 (IQR: -20 to 5) in the surgery group, compared to 0 (IQR: -20 to 10) in the GKS group (p=0.16). During the follow up period, 40.3% of patients transitioned to hospice. Overall mortality was 69.1% in the surgery group and 77.8% in the GKS group (p=0.29). Overall median post-intervention survival was 6.9 months (IQR: 2.9-12.6) among the surgery group, compared to 8.5 months (IQR: 2.8-13.4) among the GKS group (p=0.52) (Table 2).

Association Analysis

In a univariate association analysis, there was no difference in overall survival between patients undergoing surgery vs those receiving GKS to the dominant metastasis (p=0.29). Adjuvant CNS radiation post primary intervention, including additional GKS, Cyberknife (CK) or whole brain radiation therapy (p=0.007), chemotherapy (p=0.002) and immunotherapy (p<0.001) were associated with increased survival (Table 3).

Using the Cox proportional hazards model which adjusted for confounders (age, gender, primary cancer, total number of metastases, metastasis location, metastasis diameter, preoperative KPS, RPA class, additional post-intervention treatment), there was no difference in overall survival between surgery and GKS cohorts (aHR: 1.35, 95% CI:0.74-2.45, p=0.32). Pre-operative KPS (aHR: 0.97, 95% CI: 0.95-0.99, p=0.004), adjuvant CNS radiotherapy (aHR: 0.33, 95% CI: 0.19-0.56, p=<0.001), adjuvant chemotherapy (aHR: 0.27, 95% CI: 0.15-0.47, p=<0.001), and immunotherapy (aHR: 0.41, 95% CI: 0.25-0.68, p=0.001) were associated with decreased mortality (Table 3). Metastatic melanoma (aHR: 5.41, 95% CI: 1.82-16.1,
p=0.002), and other primary cancers besides breast and lung (aHR: 2.90, 95% CI: 1.15-7.27, p=0.02) were associated with increased mortality. In the sensitivity analysis, excluding patients with a dominant metastasis >3.5 cm and >3.0 cm did not lead to a difference in overall survival using the multivariate model (p=0.51 and p=0.43, respectively) (Supplemental Table 1).

Survival curves for patient undergoing surgery vs GKS as primary intervention for a dominant metastasis are represented in Figure 2a. Meanwhile, Figures 2b, 2c and 2d demonstrate survival in patients receiving adjuvant CNS radiation, chemotherapy, and immunotherapy, respectively.

Discussion

Presently there is no standardized pathway for the management of multiple brain metastases. Treatment decision-making in this population is not straightforward, as patients can present with metastases of varying size and location, and variable severity of systemic disease [6, 26]. Surgery and SRS have demonstrated favorable outcomes, both as stand-alone therapies and in combination [2, 13, 15, 18, 21, 22, 24, 26, 27]. Current CNS guidelines for the treatment of multiple brain metastases list surgical resection, WBRT and SRS as viable first-line therapies, however there are few direct comparisons of upfront resection followed by SRS versus only SRS in this setting [7, 28]. Guidelines broadly state that surgical resection or debulking could be favorable among patients with good control of systemic disease whose lesions are symptomatic and accessible by craniotomy, but patient selection is left to the discretion of treating physicians [7, 12]. Traditionally, prevailing wisdom often favors surgical resection for symptomatic dominant lesions to relieve mass effect, while SRS is reserved for lesions that are surgically inaccessible and for patients with poor control of systemic disease [29].

In this single-institution, retrospective, cohort study, we compared surgery followed by GKS with standalone GKS for patients with multiple CNS metastases and one dominant lesion and found no significant difference in survival. Moreover, quality of life was not affected by treatment modality, as KPS scores did not differ significantly at follow-up for the two cohorts. As expected, pre-intervention KPS, adjuvant chemotherapy and immunotherapy as well as adjuvant or repeat radiotherapy were associated with improved survival.

There are few series reporting outcomes on surgical resection of multiple intracranial metastases, although evidence to date suggests they are comparable to those reported for patients undergoing resection of a single metastasis [7, 18, 24, 27]. Some groups have reported a survival benefit for patients with multiple metastases if all lesions are able to be resected [2, 18, 26]. Our findings suggest that upfront SRS to multiple metastases in the setting of a dominant lesion may be as efficacious as surgery followed by GKS in achieving long-term survival. Certain patients – particularly those requiring tissue diagnosis, and those with lesions >4cm in diameter which would otherwise not be able to be adequately treated with radiation alone – should still be treated with surgery upfront [12, 30]. However, in patients not meeting these prerequisites, SRS may be preferable given its similar long term outcomes and significantly less invasive nature.
In fact, SRS can lead to dramatic size reductions in the size of a dominant lesion as seen in Supplemental Figure 1, and requires shorter recovery time and offers fewer complications compared to surgery. In fact, unlike GKS, surgery also carries the risk of post-operative complications, including infection, as shown in Supplemental Figure 2. Avoiding the need for postsurgical recovery allows for rapid initiation of systemic therapies [12, 30]. As demonstrated in our study, only preoperative functional status and systemic therapy is associated with a decrease in all-cause mortality in patients with multiple intracranial metastases. Thus, it can be inferred that initiating systemic treatment more quickly, may promote survival in this patient population.

In it important to note that in certain cases, upfront SRS may predispose patients to increased risk of death from neurological causes. These patients may require neurosurgery after SRS due to post-procedure complications, such a radiation changes or rapid progression of CNS disease, as shown in Supplemental Figure 3 [3, 7].

In recent years, there has been a move toward adopting the practice of pre-operative SRS within 48 hours of surgical resection, which is not yet common practice at UPHS. Pre-operative SRS has been shown to decrease incidence of leptomeningeal (LMD) disease progression at one year follow up [31]. This finding suggests that preoperative SRS is capable of sterilizing tumor cells that could be spilled at the time of surgery and does not confer a higher risk of LMD than WBRT, which treats the entire intracranial CSF space.

There are several limitations to our study. Firstly, our small sample size limits the strength of our findings – in fact, a combined sample of 190 patients would have been necessary to detect a statistically significant different in mortality between the two cohorts. Secondly, while patients in the GKS and surgery cohorts had no significant difference in their background characteristics, it is possible additional confounders were missed. Moreover, this study is not a perfect comparison of surgery followed by GKS versus GKS as stand-alone treatment options, as there was a selection bias toward smaller diameter of dominant metastases in the GKS cohort, although our sensitivity analysis demonstrated excluding patients with larger dominant lesions did not lead to a survival difference between the groups. Furthermore, in the study period, 20% of patients in the surgical cohort did not undergo follow-up GKS, Cyberknife, or WBRT either due to rapid progression of cancer post surgery excluding them from additional treatment or due to loss to follow up. While approximately 80% of the surgical cohort received adjuvant GKS/WBRT/CK, 20% required repeat resection, which may have influenced overall mortality as well. The high repeat resection rate and lack of universal postop radiotherapy limits the generalizability of the results. In contrast, the up-front GKS cohort rarely required late-surgery or additional GKS.

In conclusion, in this single institution, retrospective cohort study, we found no significant difference in survival or postoperative performance status between patients with multiple CNS metastases and one dominant lesion who underwent surgery followed by GKS versus standalone GKS. In patients with advanced extra-CNS disease and medical comorbidities, the additional risks of anesthesia and open surgery for a dominant lesion may not be warranted. On the basis of this single-center retrospective
analysis, SRS may offer a comparable, safer alternative for this population, and allow for the more rapid initiation of life prolonging systemic therapies.

**Declarations**

**Funding:** Not applicable.

**Conflict of Interest:** None.

**Availability of Data and Material:** All data generated or analyzed during this study are included in this published article (and its supplementary information files).

**Code Availability:** All data was analyzed and coded in Stata.

**Author Contributions:** All authors contributed to the study conception and design. MP, AG performed the data extraction and analysis. All authors have contributed to and approved the final manuscript.

**Ethics Approval:** All research was conducted in accordance with the standards of the University of Pennsylvania Institutional Review Board.

**Consent to Participate:** Not applicable.

**Consent for Publication:** Not applicable.

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Tables
Table 1. Background characteristics of patient cohort (n=129).

|                          | Total n (%) | Surgery Cohort n (%) | Gamma Knife Cohort n (%) | P-value |
|--------------------------|-------------|----------------------|--------------------------|---------|
| Age (median [IQR])       | 129 (100%)  | 84 [65.1%]           | 45 [34.9%]               | 0.25    |
| Gender                   |             |                      |                          |         |
| Female                   | 58 (47.3%)  | 43 [51.2%]           | 25 [55.6%]               | 0.64    |
| Male                     | 51 (47.3%)  | 41 [48.8%]           | 20 [44.4%]               |         |
| Primary Cancer           |             |                      |                          | 0.58    |
| Breast                   | 17 (13.2%)  | 11 (13.1%)           | 6 (13.3%)                |         |
| Lung                     | 52 (41.3%)  | 38 [45.2%]           | 24 [53.3%]               |         |
| Melanoma                 | 21 (16.3%)  | 13 [15.5%]           | 8 (17.8%)                |         |
| Other                    | 29 (22.5%)  | 22 [26.2%]           | 7 (15.6%)                |         |
| # Metastases (median [IQR]) | 3 [2-5]    | 3 [2-5]              | 3 [2-6]                  | 0.52    |
| Location of Largest Volume Met | |                      |                          |         |
| Supratentorial           | 95 (73.6%)  | 57 [67.9%]           | 38 (84.4%)               | 0.04    |
| Posterior Fossa          | 34 (26.4%)  | 27 [32.1%]           | 7 (15.6%)                |         |
| Diameter (largest metastasis, mm) (median [IQR]) | 26 [21-35] | 31 [25-38]          | 21 [20-24]               | <0.001  |
| Pre-op KPS (median [IQR]) | 80 [70-90] | 80 [70-90]          | 80 [70-90]               | 0.75    |
| RPA Class                |             |                      |                          |         |
| I                        | 43 (33.3%)  | 32 [38.1%]           | 11 [24.4%]               | 0.29    |
| II                       | 58 (42.7%)  | 41 [48.8%]           | 27 [60.0%]               |         |
| III                      | 18 (14.0%)  | 11 [13.1%]           | 7 (15.6%)                |         |
| Adjunct Treatment        |             |                      |                          |         |
| Adjuvant or Repeat Surgery | 17 (13.2%) | 15 [17.9%]          | 2 (4.4%)                 | 0.03    |
| Adjuvant or Repeat Radiotherapy | 34 (65.1%) | 66 [78.6%]          | 18 (40.0%)               | <0.001  |
| Chemotherapy             | 92 (71.9%)  | 56 [68.7%]           | 35 (77.8%)               | 0.27    |
| Immunotherapy            | 80 (62.0%)  | 53 [63.1%]           | 27 [60.0%]               | 0.73    |

Table 2. Outcomes of interest (n=129).

| Outcomes                             | Total n (%) | Surgery Cohort n (%) | Gamma Knife Cohort n (%) | P-value |
|--------------------------------------|-------------|----------------------|--------------------------|---------|
| Follow Up, months (median [IQR])     | 23 [10-50]  | 23.5 [10-61]         | 22 [14-36]               | 0.73    |
| Change in KPS                        | -0.10 [-20-10] | -0.10 [-20-5]       | 0 [-20-10]               | 0.16    |
| Hospice                              | 52 (40.3%)  | 34 (40.5%)           | 18 (40.0%)               | 0.96    |
| Overall Mortality                    | 93 (72.1%)  | 58 (69.1%)           | 35 (77.8%)               | 0.29    |
| Post-intervention Survival, months (median [IQR]) | 7.4 [2.8-13.0] | 6.9 [2.9-12.6] | 8.5 [2.8-13.4] | 0.52    |
Table 3. Factors associated with mortality (n=129).

|                         | Outcome | P-value | Adjusted HR [95% CI] | P-value |
|-------------------------|---------|---------|----------------------|---------|
|                         | Dead, n (%) | Alive, n (%) |                     |         |
| Total                   | 93 (72.1%) | 35 (27.9%) |                     |         |
| Age (median [IQR])      | 60 [53-67] | 60.5 [51-65] | 0.57                | 0.99 (0.97-1.01) | 0.38 |
| Gender                  |         |         |                     |         |
| Male                    | 44 (72.1%) | 17 (27.9%) | 0.99                | 1.15 (0.71-1.86) | 0.56 |
| Female                  | 49 (72.1%) | 19 (28.0%) | 0.99                | 1.15 (0.71-1.86) | 0.56 |
| Primary Cancer          |         |         |                     |         |
| Breast                  | 10 (58.8%) | 7 (41.2%) | 0.49                | 1.78 (0.71-4.47) | 0.22 |
| Lung                    | 47 (75.8%) | 15 (24.2%) | 0.49                | 5.41 (1.82-16.1) | 0.002 |
| Melanoma                | 14 (66.7%) | 7 (33.3%) | 0.49                | 2.90 (1.15-7.27) | 0.02 |
| Other                   | 22 (75.9%) | 7 (24.1%) | 0.49                | 1.02 (0.98-1.05) | 0.37 |
| # Metastases (median [IQR]) | 3 [2-5] | 3 [2-4.5] | 0.93                | 1.02 (0.98-1.05) | 0.37 |
| Location of Largest Volume Met |       |         |                     |         |
| Supratentorial          | 66 (69.5%) | 29 (30.5%) | 0.27                | 1.23 (0.70-2.14) | 0.47 |
| Posterior Fossa         | 27 (79.4%) | 7 (20.6%) | 0.27                | 1.23 (0.70-2.14) | 0.47 |
| Diameter (largest metastasis, mm) (median [IQR]) | 26 [21-34] | 26 [21-28] | 0.7 | 0.99 (0.97-1.01) | 0.44 |
| Pre-op KPS (median [IQR]) | 80 [70-50] | 80 [70-95] | 0.12                | 0.97 (0.95-0.99) | 0.004 |
| RPA Class               |         |         |                     |         |
| I                       | 33 (76.7%) | 10 (23.3%) | 0.68                | 0.76 (0.48-1.20) | 0.24 |
| II                      | 47 (69.1%) | 21 (30.9%) | 0.68                | 0.76 (0.48-1.20) | 0.24 |
| III                     | 13 (72.2%) | 5 (27.8%) | 0.68                | 0.76 (0.48-1.20) | 0.24 |
| Adjunct Treatment       |         |         |                     |         |
| Adjuvant or Repeat Surgery | 14 (82.4%) | 3 (17.7%) | 0.31                | 0.85 (0.43-1.67) | 0.64 |
| Adjuvant or Repeat Radiotherapy | 54 (64.3%) | 30 (35.7%) | **0.007** | 0.33 (0.19-0.56) | <0.001 |
| Chemotherapy            | 59 (64.3%) | 33 (35.9%) | **0.002** | 0.27 (0.15-0.47) | <0.001 |
| Immunotherapy           | 48 (60.0%) | 32 (40.0%) | **<0.001** | 0.41 (0.25-0.68) | <0.001 |
| Intervention            |         |         |                     |         |
| Gamma Knife             | 35 (77.8%) | 10 (22.2%) | 0.29                | 1.35 (0.74-2.45) | 0.32 |
| Surgery                 | 58 (69.1%) | 26 (31.0%) | 0.29                | 1.35 (0.74-2.45) | 0.32 |

Figures
Figure 1

Screening for surgical patients cohort.
Figure 2

Post-intervention survival in patients comparing various interventions.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistcohort.docx
- SupplementalFigures.docx
- SupplementalTable1.docx