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Case study

Postoperative radiosurgery for the treatment of metastatic brain tumor: Evaluation of local failure and leptomeningeal disease

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A B S T R A C T

In patients undergoing surgical resection of a metastatic brain tumor, whole brain radiation therapy reduces the risk of recurrence and neurologic death. Focal radiation has the potential to mitigate neurocognitive side effects. We present an institutional experience of postoperative radiosurgery for the treatment of brain metastases. A retrospective review of a prospectively maintained institutional radiosurgery database was performed for the years 2005–2015 identifying all adult patients treated with postoperative radiosurgery to the tumor bed. Primary endpoints include local recurrence and postoperative LMD. Kaplan-Meier curves and Cox regression were used to evaluate time to local recurrence and postoperative LMD. Ninety-one patients received adjuvant focal radiation for a brain metastasis. Median radiographic follow-up among patients who had not developed a local failure was 9 months. Of the 91 patients, 20 (22%) developed local recurrence and 32 (35%) experienced postoperative LMD. Freedom from local recurrence and LMD at 1 year was 84% and 69%, respectively. In multivariable models, predictors of local failure included the presence of more than one brain metastasis (HR = 2.65, p = .04) with a preoperative tumor diameter of >3 cm (HR = 4.16, p = .06) trending toward significance. There was a trend to a higher risk of LMD with >1 tumor (HR 2.07, p = .06) and breast cancer (HR 2.37, p = .07). More than one metastasis is an independent predictor of local and leptomeningeal failure following postoperative radiosurgery. The high rate of LMD was likely related to the liberal definition of LMD to include focal dural recurrences.

1. Introduction

Brain metastases are the most common central nervous system malignancy with an estimated prevalence among cancer patients of 10% [1–3]. The incidence of brain metastases is increasing, likely due to closer surveillance, improved control of systemic cancer, and prolonged survival [4]. Their presence portends a poor prognosis with survival generally measured in weeks-months [2]. Current National Comprehensive Cancer Network guidelines recommend a combination of surgery and radiation for the treatment of resectable lesions with reasonable systemic treatment options [5].

Following two landmark trials by Patchell et al., surgical resection followed by whole brain radiation therapy (WBRT) became the most widely accepted paradigm for the treatment of solitary or oligometastases [6,7]. The addition of WBRT to surgical resection reduced tumor recurrence and was associated with a lower rate of neurologic death [7]. However, WBRT subjects a large volume of normal tissue to therapeutic radiation doses and has been associated with deleterious neurocognitive sequela [8–10]. As treatment has become more individualized, there has been an emphasis on balancing treatment efficacy against neurotoxicity, especially in patients with a good prognosis [4].

The equivalent overall survival and superior neurocognitive outcomes of stereotactic radiosurgery (SRS) alone versus WBRT plus SRS for the treatment of intact brain metastases [8,11,12] has led some physicians to prefer focal radiation as first line for the adjuvant treatment of resected brain metastases. We present an institutional experience of postoperative radiosurgery for the treatment of brain metastases with a focus on local failure and leptomeningeal disease.

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2. Materials and methods

2.1. Patient selection

A retrospective review of a prospectively maintained radiosurgery database was performed at a single academic institution for the years 2005–2015 identifying all patients treated with postoperative radiosurgery. Given the concern for cognitive impairment following whole brain radiation therapy (WBRT), the preferred modality for adjuvant radiation at this institution is radiosurgery. Thus, all adult patients undergoing surgical resection of a brain metastasis were treated with radiosurgery to the surgical cavity in the absence of extenuating circumstances (i.e. unexpected death, innumerable metastases, change in goals of care, loss to follow up). Inclusion criteria: adult patient with a newly diagnosed intracranial metastasis treated with surgical resection (gross total or subtotal resection) followed by postoperative radiosurgery (single or hypofractionated treatment regimen) to the tumor bed. Exclusion criteria: age <18 years, radiosensitive tumor pathology (small cell lung cancer and lymphoma), prior WBRT, biopsy as only surgical intervention, pathology consistent with primary brain tumor, lack of radiographic follow up, and lack of clinical follow up. The records of included patients were reviewed and the following data was collected: age, sex, pathology of intracranial metastasis, number of metastases, size of index metastasis (tumor undergoing resection and postoperative radiation), location of index metastasis, presence of preoperative leptomeningeal involvement, date of surgery, surgical result (gross total vs subtotal resection) date of radiosurgery, radiosurgery dose and schedule, adverse events, radiographic follow up, and clinical follow up. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

2.2. Radiosurgery technique

All patients received either Gamma Knife radiosurgery (model B or C) or linear accelerator (LINAC) radiosurgery with a VMAT technique. The modality of choice has transitioned gradually from predominantly Gamma Knife to predominantly LINAC over the last 2–3 years of included cases. Initially, larger cavities were preferentially treated with LINAC due to efficiency and the ability to hypofractionate treatment. The decision to treat patients with a single fraction or hypofractionated dose schedule was based upon maximum diameter greater than 3–4 cm. LINAC patients received either a single dose of radiation or five fractions of 5–6 Gy (total 25 Gy or 30 Gy); Gamma Knife was delivered as a single dose of radiation. Median dose single fraction treatment was 16 Gy (range 10–20 Gy; mean 15.9 Gy). The target volume in all cases was the cavity without an additional margin. GKS was typically prescribed to the 50% isodose line. LINAC treatment was prescribed to the isodose line that covered 99–100% of the target with typical hotspots of 30–80% beyond the prescription dose allowed. Dose heterogeneity was not penalized in the cost function of the LINAC plans. LINAC delivery was with 2–4 arcs with a 2400 MU/min flattening filter free mode utilizing TrueBeam STX and the HD-120 multi-leaf collimator with a central leaf resolution of 2.5 mm. LINAC patients were treated frameless with KV and cone beam CT (CBCT) image guidance for alignment; localization accuracy of KV and CBCT was within 1 mm. Additional details of the single isocenter VMAT planning and delivery have been published [13]. Radiosurgery timing depended on the volume of the post-operative cavity and plans to integrate radiosurgery with systemic therapy. Patients were generally treated based upon a treatment planning MRI performed postoperative day 1 (treatment within 2 weeks of surgery) or based upon MRI at one month follow-up (treatment generally within 5–6 weeks of surgery).

2.3. Radiographic definitions

Intracranial metastases were initially diagnosed with contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with the typical findings of a contrast enhancing lesion with surrounding vasogenic edema. The number of intracranial metastases were totaled at the time of radiosurgery. Size of the index tumor was reported at the maximum diameter on axial imaging in centimeters (cm). Location of the index metastasis was reported as supratentorial or infratentorial. The presence of preoperative leptomeningeal involvement was defined as any metastasis that contacts a leptomeningeal surface; this includes a superficial metastasis that abuts arachnoid and dura without obvious dural enhancement. Gross total resection was defined as lack of contrast enhancing mass on postoperative imaging.

Local failure was defined as the development or progression of nodular contrast enhancement within 5 mm (mm) of the index metastasis. Subsequent operative interventions within 5 mm of the index tumor cavity that resulted in pathologic specimens consistent with tumor were also considered local failure. Diffuse tumor cavity enhancement or nodular enhancement that resolved on subsequent imaging was considered treatment effect. Postoperative leptomeningeal disease (LMD) was defined as focal or diffuse leptomeningeal enhancement of the brain, spinal cord, or cauda equina, dural enhancement beyond 5 mm from the index metastasis, subependymal enhancement, and enhancement of cranial nerves (Fig. 1).

Imaging, clinic notes, and radiology reports regarding local failure were reviewed by the lead author (PMF). In cases of ambiguity, the imaging, clinic notes, and radiology reports were then reviewed with senior authors (JMM and JBF) for a final determination. All cases of potential postoperative LMD (imaging, clinic notes, and radiology reports) were reviewed by three authors (PMF, JMM, and JBF) for final determination.

2.4. Follow up

Brain metastasis patients are routinely followed by a combination of oncology, radiation oncology, and neurosurgery with contrast enhanced MRIs obtained on postoperative day 1 and then at 3 month intervals. Date of last follow up was considered to be the last time a patient was formally evaluated by a physician in one of these three fields. Important to note, follow up was capitated at the time of WBRT with the first day of treatment considered the last day of follow up. Days from treatment to local failure or postoperative LMD was calculated from the date of surgical resection to the date of imaging diagnosis. Adverse events were defined by the Common Terminology Criteria for Adverse Events Version 4.0 and included grade 4 or 5 neurologic events, grade 3 or higher seizure, grade 4 or 5 dermatologic event, or grade 3 or higher wound complication.

2.5. Statistical analysis

Descriptive statistics are presented for the overall sample in terms of frequencies and percentages for categorical variables and median, minimum, and maximum for continuous variables. The Kaplan-Meier approach was used to plot survival curve estimates for both days from surgery to Local Failure and LMD time-to-event outcomes. Bivariate associations between time-to-event outcomes and patient characteristics were assessed using log-rank tests for strata homogeneity. In addition to this, we used multivariable Cox regression in order to estimate the Hazard Ratios