



Proton beam radiosurgery: early clinical results

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Comment on: Atkins KM, Pashtan IM, Bussi  re MR, *et al.* Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis of 370 Patients. *Int J Radiat Oncol Biol Phys* 2018;101:820-9.

Submitted Nov 01, 2018. Accepted for publication Nov 14, 2018.

doi: 10.21037/tcr.2018.11.17

View this article at: <http://dx.doi.org/10.21037/tcr.2018.11.17>

Introduction

Brain metastases are the most common type of intracranial malignancy. Brain metastases are a devastating effect of cancer which lowers the quality of life of patients and can eventually lead to their death. There are certain cancers which commonly metastasize to the brain, including lung cancer, breast cancer, melanoma, and renal cell carcinoma. The management for patients with brain metastases can vary widely and includes neurosurgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), systemic therapy, or comfort care measures alone (1-3). Untreated, the median survival of a patient with brain metastases from a solid malignancy is 1 to 2 months.

Several photon-based SRS platforms are in widespread clinical use including Gamma Knife (Elekta AB, Stockholm, Sweden), Cyberknife (Accuray, Sunnyvale, CA, USA), and linear-accelerator based (LINAC) radiosurgery (4). In the study "Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis of 370 Patients", the authors evaluate the effectiveness of proton beam SRS for patient with brain metastases (5). Proton therapy could allow for improved normal tissue sparing because of its physical characteristics. Proton particles deposit a majority of their energy in a sharp peak, known as the Bragg peak, at specified depths in tissue. This allows for lower radiation of healthy tissue distal to the tumor along the beam path. Cranial targets were the first recorded treatments with proton and ion beams. While used commonly in patients with skull base and pediatric tumors, the use of proton therapy for SRS is less common.

Proton SRS

Atkins *et al.* retrospectively evaluated 370 patients with 815 metastases who were treated with proton SRS. Patients evaluated received proton therapy between April 1991 and November 2016 at the Harvard Cyclotron Laboratory or the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital. Patients included in this study were patients with diagnosed brain metastases who received single-fraction proton SRS and had at least 1 contrast enhanced MRI scan (CT if MRI contraindicated).

Patients were prepared for treatment with either a rigid frame with external skull fixation or a thermoplastic mask. Dose planning was performed using CT scan and was typically prescribed to the 90% isodose line. Local and distant brain failures and radionecrosis were determined by review of medical records. Acute toxicities were defined as occurring within 8 weeks after proton SRS and graded according to the CTCAE. Local failure, distant brain failure and pathologic radionecrosis were calculated using the Fine and Gray method to modify for competing risk of death; Kaplan-Meier curves were used for survival.

The median follow-up from the time of first proton SRS was 9.2 months. The most common primary histologies included non-small cell lung carcinoma (NSCLC) (126 patients, 34.1%), melanoma (104 patients, 28.1%), and breast carcinoma (64 patients, 17.3%). Most patients had a Karnofsky Performance Status (KPS) of 80–100% (250 patients, 67.6%). More than half of the patients had received prior cranial radiotherapy (203 patients, 54.9%), with 184 (49.7%) patients receiving prior WBRT. The

median number of lesions treated per patient was 2, the median volume of the lesion was 0.6 cm³, and the median delivered proton SRS dose was 18 Gy. The majority of lesions were not treated with concurrent chemotherapy or immunotherapy (574 metastases, 70.4%).

The cumulative incidence of local failure at 6 and 12 months was 4.3% (95% CI, 3.0–5.9%) and 8.5% (95% CI, 6.7–10.6%), respectively. Distant failure at 6 and 12 months was 39.1% (95% CI, 34.1–44.0%) and 48.2% (95% CI, 43.0–53.2%), respectively. Median overall patient survival was 12.4 months following SRS, and the overall survival at 6 and 12 months was 76.0% (95% CI, 71.3–80.0%) and 51.5% (95% CI, 46.3–56.5%), respectively. In the multivariate analysis, the only factor which had a significant effect on lowering the risk of local failure was previous radiation therapy (RT) (HR 0.62, 95% CI, 0.41–0.93; P=0.021). Of the 221 patients who developed distant brain failure, more than half received subsequent focal RT including fractionated RT (9 patients, 4.1%) and SRS (126 patients, 57%); patients also received WBRT (33 patients, 14.9%), chemotherapy (12 patients, 5.4%), and surgery (3 patients, 1.4%). There were no acute severe toxicities (grade 4 or 5) within 8 weeks of therapy. Among the 370 patients, grade 1 to 3 CTCAE toxicities occurred in 40.5% of patients (n=150). The majority of these patients experienced grade 1 toxicity (109 patients, 72.7%), followed by grade 2 (22 patients, 14.7%), and grade 3 (19 patients, 12.7%) in the minority of patients.

Implications

In 1990, Patchell *et al.* from the University of Kentucky established surgical resection as a mainstay of the initial treatment of patients with a single brain metastasis (6). Since that time, there has been a steady drift toward SRS for similar patients with limited brain metastases (either after resection or for definitive therapy). This is, in part, due to a concern regarding neurocognitive deficits associated with WBRT (7,8).

Protons and heavier charged particles are appealing choices for brain irradiation because of their dosimetric properties. They have well defined ranges and deposit the majority of their energy at their maximum depth, the Bragg peak, allowing for dose escalation within the target. In contrast to photon irradiation, after the Bragg peak, there is essentially no exit radiation dose (9). These properties allow proton SRS to have potentially less of an effect on adjacent normal healthy brain tissue, while still affording tumor

ablation. It is important to note however, that volumetric expansions to account for intrafractional motion, etc. could also have a dramatic impact on normal tissue irradiation. In the case of small field proton beam irradiation, there exists additional physical uncertainties that could require a further expansion into normal brain tissue to account for these unknowns.

For this study, it is important to note that many patients had received prior treatment including WBRT, SRS, chemotherapy, and surgical resection. Therefore, extrapolation of proton SRS to newly diagnosed brain metastases should be done with caution. Additionally, baseline patient heterogeneities exist (such as changes in systemic therapy effectiveness over this time period), which could limit statistical comparisons in this retrospective study. Regardless, the authors demonstrate in a relatively large patient population that proton SRS can be safely performed at a center with expertise, with careful consideration of the physical uncertainty of proton beam delivery (depth uncertainty, small field limitations, plan robustness, etc.).

Patients with brain metastases are unfortunately common in today's oncology practice, with an increasing incidence over recent decades owing to improvements in systemic therapy and MRI screening (10). We commend these authors for demonstrating that proton SRS is deliverable with comparable clinical outcomes and acceptable toxicity. Where do we go from here? A larger societal question at hand concerns the impact of the widespread adoption of proton SRS. We should consider whether proton radiosurgery will offer a meaningful therapeutic advantage to photon radiosurgery (either through improved local control or through reduced toxicity) over their generally limited life span. With similar volumes and prescriptions, proton SRS is only likely to meaningfully improve outcomes in a select patient population (tumor abutting critical structures, re-irradiation, etc.), particularly when considering the physical uncertainties with small field proton dosimetry. As proton therapy remains a limited resource throughout the world, care should be taken to ensure that patients are prioritized appropriately with this technology. In the future, it is likely that proton beam therapy will become more widespread internationally, and at that time study's such as this one will be critical to furthering the radiosurgical field.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (Shanghai Proton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.11.17>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Leon J, Peterson J, Hadley A, Vallow L, Trifiletti DM. Proton beam radiosurgery: early clinical results. *Transl Cancer Res* 2019;8(Suppl 2):S115-S117. doi: 10.21037/tcr.2018.11.17