The Role of Radiosurgery in the Management of Brain Metastases

a report by
David Roberge, MD

Assistant Professor, Radiation Oncology, McGill University

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It was decades after the introduction of the first concept of stereotactic radiosurgery (SRS) at the Karolinska Institute[1] that stereotactic irradiation began to see widespread use in the treatment of brain tumors. Despite many technical changes since the 1950s, radiosurgery remains a radiotherapy technique characterized by accurate delivery of high doses of radiation in a single session to small, stereotactically defined targets with sharp dose fall-off outside the targeted volume. Such a treatment appears ideally suited to parenchymal brain metastases—tumors geographically well delimited with minimal infiltration into the adjacent brain.[2] Unfortunately, such metastases are a common occurrence, representing approximately 250,000 cases per year in the US alone.[3] Thus, even if only a fraction of these patients are referred for SRS, the management of brain metastases invariably represents a significant fraction of the workload of a radiosurgery practice. Until recently most reports supporting the use of SRS were retrospective case series. This has changed with the publication of randomized trials characterizing the benefits of SRS in the management of newly diagnosed brain oligometastases.

Newly Diagnosed Brain Metastases

Patients with newly diagnosed brain metastases have poor local control after whole-brain radiation (WBRT). Even when intra-cranial disease is limited, neurological death occurs in approximately one-third of patients. These facts underlie the investigation of SRS as an addition to WBRT. In a small trial limited to patients with 2–4 metastases—all ≤25mm in mean diameter—Kondziolka et al. randomized patients to WBRT alone (30Gy in 12 fractions) or WBRT with SRS.[4] The trial was closed prematurely when the primary end-point—local control—was achieved after the first 27 patients were enrolled. Local control was 0% at one year in the control arm, well below what is expected. Overall survival was not different between the two arms (median 7.5 months for WBRT and 11.0 months for WBRT plus SRS) and there was no information regarding treatment toxicity or quality of life. In a second small and, as yet, unpublished trial, Chougule et al. randomized patients to three treatment strategies: WBRT (30Gy in 10 fractions), WBRT plus SRS, and SRS alone.[5] Patients were eligible if they had ≤3 metastases, tumor volume ≤30cc, and a life expectancy of three months. Ninety-six patients received the allocated treatment and were part of the analysis. Approximately half of the patients underwent resection of a large symptomatic lesion prior to randomization. In looking specifically at the issue of adding SRS to WBRT, local control was improved from 62 to 91%, but median overall survival was unchanged (five months for the combination and nine months for WBRT alone). In what is to be the definitive trial of SRS as a focal boost to WBRT, the Radiation Therapy Oncology Group (RTOG) accrued patients in a trial of WBRT (37.5Gy in 15 fractions) versus WBRT followed by SRS (RTOG 95-08).[6] From 1999 to 2001, 333 patients were randomized. Eligible patients had 1–3 metastases (the largest ≤4cm), were not surgical candidates, and had a Karnofsky Performance Status score of ≥70. The primary end-point of the trial was overall survival with a planned analysis for patients with a single lesion. Overall, the trial did not find a significant advantage in overall survival (6.5 versus 5.7 months, p=0.13), but did show an improvement in survival for patients with a single lesion (6.5 versus 4.9 months, p=0.04). The less likely a patient is to die from extra-cranial disease, the more he or she is expected to benefit from aggressive central nervous system (CNS)-directed therapy. This was shown in various subgroup analyses. For example, young patients (age <65) having controlled primary tumors and no other metastases had a median survival of 11.6 months with WBRT plus SRS versus 9.6 months for WBRT. The trial also confirmed that SRS can be performed safely, only adding 3% grade III–IV acute and late toxicity.

Recurrent Brain Metastases

Patients with recurrent or progressive brain metastases have limited treatment options. Although there is no high-level evidence supporting the use of radiosurgery in these patients, retrospective series of selected patients report median overall survival times similar to those expected for patients treated at initial presentation (6–10 months).[7,8] Most patients in these series have been treated for 1–3 metastases, but patterns of practice vary widely. For reasons including patient and physician preference, it is unlikely that the benefit of radiosurgery in this setting will ever be tested in a randomized trial.

Controversies

Surgery versus Radiosurgery

Now that randomized studies support a survival advantage to adding either surgery or radiosurgery to WBRT in the treatment of solitary brain metastases, clinicians and patients must often choose between the two modalities. In some cases the choice is obvious: SRS is preferred for lesions in eloquent or surgically inaccessible areas while surgery is chosen for lesions too large for SRS (>4cm) or in patients lacking a pathological diagnosis. For other cases, the advantages and disadvantages of the two modalities are weighed in the context of the individual patient. Surgery offers immediate relief of mass effect, reduced steroid use, and a pathological diagnosis. On the other hand,

David Roberge, MD, is an Assistant Professor of Radiation Oncology at McGill University. In the late 1980s the McGill team was pioneering in developing linear accelerator-based radiosurgery in North America. This team is well known for the development of dynamic stereotactic radiosurgery, as well as for early work on fractionated stereotactic radiotherapy. They continue to be prominent in multi-institutional trials of radiosurgery. Dr Roberge's own clinical and academic interests include intra- and extra-cranial stereotactic irradiation. Radiosurgery is a prominent subject of his book chapters, scientific papers, and visiting professorships. Sponsored by Schering Canada, he is the principal investigator of a phase I trial of chemosensitized radiosurgery for recurrent brain metastases.

radiosurgery is a non-invasive outpatient procedure without risk for leptomeningeal tumor seeding. There have been unsuccessful attempts to obtain class I evidence to guide us in cases for which both treatments are reasonable. At this time patients are still being enrolled in a phase III trial.

Whole-brain Radiotherapy

"Suddenly a solitary horseman appeared on the horizon, then another, then another, and then six. In a few moments a whole crowd of horsemen swooped down upon him." Stephen Leacock lived a stone's throw from the Montreal General Hospital and authored this passage without suspecting that it would apply to the subject of oligometastases.[9] As with the horsemen, brain metastases are unrelenting, and truly cured patients are a rarity. If they are afforded a long enough reprieve from their extra-cranial disease, approximately 80% of patients treated without WBRT will have progressive intra-cranial disease. It has now been demonstrated in two trials that WBRT can decrease the occurrence of new brain metastases. In the three-arm trial of Chougule et al., the development of new brain metastases was halved by the use of WBRT (19–23 versus 43%).[5] In a second recently published multicenter trial, 132 patients were randomized to SRS versus WBRT (30Gy in 10 fractions) plus SRS.[10] The use of WBRT decreased the one-year rate of brain tumor recurrence from 76.4 to 46.8% ($p<0.001$), but did not improve overall survival (38.5 versus 28.4% at one year, for WBRT plus SRS and SRS, respectively ($p=0.42$). A third, smaller trial failed to complete accrual. This Trans-Tasman Radiation Oncology Group trial randomized patients post-surgery or -radiosurgery to WBRT (30–36Gy) versus observation. Despite a large difference in CNS relapse (30 versus 78%), this was not statistically significant as only 19 patients were enrolled. With only 20–30% of oligometastatic patients suffering a neurological death, current published trials are all underpowered to detect any survival advantage that could reasonably be expected to result from even a 50% decrease in new brain metastases. After an initial failed effort by the American College of Surgeons Oncology Group (ACOSOG), two groups—the European Organization for Research and Treatment of Cancer (EORTC) and the North Central Cancer Treatment Group (NCCTG)—are currently taking up this issue with larger projected sample sizes (340 and 528 patients). At this time, what can be asserted with confidence is that WBRT significantly reduces the risk of developing new metastases. Despite regular imaging, patients in whom WBRT is withheld will most commonly have symptomatic recurrences. They have a five-fold risk of needing salvage treatment and not all patients will be amenable to second-line focal therapy.[11] Whether these risks are offset by the—mostly unquantified—toxicities of WBRT is a matter of hot debate.

Management of 'Radio-resistant' Tumors

With few exceptions, in the absence of histology-specific interventions, treatment of brain metastases tends to be decided with little concern as to the nature of the primary tumor. As an example, RTOG 95-08 was open to all primary tumors with the exception of hematological malignancies.[6] Despite generally broad eligibility criteria, two-thirds of patients in most trials have non-small-cell lung cancer (NSCLC). Thus, expanding the conclusions of current trials to less common histologies might not be appropriate. In a review of 189 patients treated with SRS for 'radioresistant' tumors, the one-year actuarial local control was 52%.[12] In keeping with other published series, the local control in this group was better for renal cell carcinoma and worse for patients with melanoma or sarcoma. The role of WBRT is undefined in these patients. Although new brain metastases are common, good evidence that they can be prevented by WBRT is lacking.

Radiosurgery Trends

Fractionation

To any radiobiologist, the choice of a single fraction of radiation to control an epithelial tumor is counterintuitive. Not to fractionate is to miss an opportunity to differentially spare normal tissue and allow necrotic tumors to re-oxygenate and cancer cells to redistribute into more sensitive phases of the cell cycle. These radiobiological disadvantages have been partially offset by the steep dose gradient limiting radiation exposure of healthy brains as well as the potential effect of high single doses on tumor vasculature. It remains that, to avoid toxicity, SRS doses must be decreased for metastases larger than 2cm. In these tumors, the actuarial local control is disappointing, a fact masked by reporting crude data in patients with short survival. In a series from the Cleveland clinic, one-year local control rates were 45 and 49% for lesions treated with 15 and 18Gy, respectively.[13] Until recently, because of the need for rigid frames affixed to the patient's skull, stereotactic accuracy had been mostly limited to single fraction treatments. Newer technologies in image-guided radiotherapy now permit SRS positioning accuracy without the use of an invasive frame.[14] This allows convenient fractionation of the dose, possibly leading to better local control for lesions >2cm and making larger lesions amenable to focal radiotherapy. Another strategy made possible by new technology is the so-called concurrent boost approach, in which individual tumors are 'boosted' during the delivery of WBRT.[15]

Surgery, SRS, WBRT, and the Kitchen Sink

For patients managed with surgical resection, the surgical bed is an important site of failure—even with adjuvant WBRT. This has been an opportunity to investigate SRS as a complement or alternative to WBRT.[16] When used alone, it may be more logical to fractionate the dose as, in contrast to traditional SRS, what is treated is mostly normal brain tissue.

Targeted Therapy/Chemotherapy

As targeted small molecules and blood–brain-barrier-crossing cytotoxic agents enter the therapeutic armamentarium for a growing number of malignancies, the agents will complement and even compete with radiosurgery.[17] The current RTOG trial for NSCLC brain oligometastases is currently investigating two such agents: temozolomide and erlotinib. At McGill University, chemosensitization is under investigation for patients treated with SRS alone in the context of recurrent brain metastases.

Conclusions

SRS is an important tool in the management of selected patients with intra-cranial metastases. The technology is evolving and its use continues to be refined through prospective clinical trials. ■

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