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Radiosurgery of brain metastases — How many is too many?

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As technology for the radiosurgical treatment of brain metastases has evolved, it is now technically and logistically possible to treat an increasingly larger number of brain metastases. Historically, it was difficult to treat more than three or four tumors. For this reason and a perception that patients with more than a few tumors had dramatically worse survival, large clinical trials limited the eligibility to those with no more than three to four tumors[1]. The earlier model Gamma Knife units were designed and optimized for a single target in the brain and could not reach the entire cranial volume for any given frame placement. The newer model Gamma Knife units (Perfexion™ and Icon™) were designed to more easily treat multiple tumors anywhere in the brain. New linear accelerators offer single isocenter therapies for multiple targets accurately aligned with automated six degree of freedom image guidance systems. Efficient delivery is enhanced by VMAT and high output flattening filter free modes offering up to four times the beam fluence of standard linacs. Taken together these enhancements in technology bring the possibility of radiosurgery to a greater percentage of patients with brain metastases. As there is increasing concern regarding the neurocognitive consequences of whole brain radiation therapy, we need to ask *"how many is too many?"* To begin to answer this question, it is useful to revisit some of the potential misconceptions regarding brain metastases.

Does the number of brain metastases predict survival such that we should treat patients with more than three or four metastases differently?

Many studies have examined prognostic factors for overall survival in patients with brain metastases and have identified tumor number as a prognostic factor. It is clear that patients with a single brain metastasis live longer than those with more than one. It is not so clear that patients with two or three tumors have a different prognosis than those with five or seven. In one of the largest prospective trials of radiosurgery ever published, Yamamoto et al treated 1194 patients with 1-10 metastases with radiosurgery alone[2]. There was no difference in overall survival for those with 2-4 tumors vs. those with more. This study suggests that tumor number alone is not a reason to exclude a patient from treatment with radiosurgery alone.

Is the treatment of a high number of brain metastases dosimetrically equivalent to giving whole brain radiation therapy?

In a recent dosimetric analysis, Becker et al found that approximately 40 tumors of mixed sizes were required to reach a mean whole brain radiation dose of 8 Gy[3]. The number of tumors required to reach 8 Gy equivalent was heavily dependent upon tumor size. In fact, 177 tumors 4 mm or less in diameter could be treated to be equivalent to 8 Gy whole brain. Other investigators have found mean brain doses for Gamma Knife or modern linac techniques to be typically less than 2-3 Gy for multiple targets consistent with the above dosimetric simulations[4,5].

Do all patients with a higher number of brain metastases quickly develop distant brain failure?

In prospective randomized trials and multi-institutional series the risk of distant brain failure after

treatment of 1-4 tumors varies from 44-63% at one year[6-8]. Distant brain failure is predicted by many variables including histology, number of tumors, and state of systemic disease control. Molecular predictors of distant brain failure have been identified in subsets of breast cancer and melanoma. In the large prospective trial by Yamamoto, there was no statistically significant difference in distant brain failure between patients that had 2-4 tumors treated vs. more, although a non-statically significant trend was present[2].

NCCN guidelines no longer include tumor number as a contraindication to radiosurgery. Many factors may influence the decision to offer radiosurgery including disease status, performance status, and the ability to integrate radiation therapy into systemic therapy plans. It is clear that this is no longer a technical question, but rather a clinical question. Prospective trials are needed for the "more than four" subgroup to better define optimal care. Lessons from the past have taught us that there is unlikely to be an overall survival difference, but that other measures such as quality of life and neuro-cognition are important study endpoints in future disease-specific (or molecular subset) trials.

Authors' disclosure of potential conflicts of interest

The authors reported no conflict of interest.

Author contributions

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