

## *Swedish Medical Center*

### *Cerebral Metastasis*

Cerebral metastasis will become a clinical problem in approximately 30% of patients with cancer diagnosed in 2004, leading in many to significant symptoms, morbidity or death. One or more brain metastasis will be detected in at least 120,000 patients this year, with some estimates as high as >200,000 patients. Lung cancer is the leading primary site, with breast cancer; GI, GU malignancies and melanoma make up the majority of the remainder.

High quality contrasted brain MRI is the diagnostic test of choice for evaluation, with only about one of three patients having a solitary metastasis, 50% having up to 2 mets with the majority of these being supratentorial. Survival untreated is a median of only seven weeks, however the patient performance status (Karnofsky score), histologic type of cancer, patient age, presence of non-CNS disease and the treatment performed all have a significant impact on survival.

The Radiation Therapy Oncology Group (RTOG) was able to partition patients with brain mets into three prognostic categories through extensive analysis of over 1,000 enrollees in three randomized clinical trials performed 1979-1993. The best group with respect to survival were younger patients with a KPS of >70, a controlled primary and no non-CNS metastasis. The poorest survival occurred in patients with a poor performance status. In many reported series, approximately 10-15% of patients survive greater than one year and occasionally much longer and it is this cohort in which aggressive treatment strategies might make a significant impact.

With improved patient selection and systemic treatment of extra cranial disease, a reasonable goal might be to attempt to increase this cohort to 25-30% of the total. To accomplish this will require improved strategies to control the brain disease itself. Historically, steroids, whole brain radiotherapy (WBRT), and surgical metastasectomy have been the primary modalities, with stereotactic radiosurgery and chemotherapy having gained acceptance more recently. Controversies which have arisen revolve around which patients deserve more aggressive management such as surgery or radiosurgery and when, if ever, it might be appropriate to omit WBRT, thereby avoiding its toxicity.

One principal argument for WBRT has been that the majority of patients present with 3 or more mets and it is therefore necessary to treat all of these, and certainly in individuals presenting with multiple metastasis, that is the indicated first line therapy. Recent data suggests that in a patient presenting with only a single metastasis on initial MRI, there is a ~70% likelihood that there is no other brain disease and that omission of WBRT might be reasonable if the incident metastasis can be successfully excised or treated with Gamma Knife™ Radiosurgery (GKRS). When WBRT is eventually employed, the use of more protracted dose/fractionation schedules has been shown to improve longer term neurocognitive functioning in brain metastasis survivors. A patient in whom WBRT is omitted must be reliably followed up with careful and regular surveillance with MRI, so as to successfully salvage the approximately 1/3 who will develop brain relapse and require radiation to the whole brain at that time.

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### *Cerebral Metastasis (continued)*

There is ample data in the published literature, including phase III, randomized trial data, to support the aggressive use of more invasive strategies to eradicate the obvious, visible metastasis seen on initial imaging, providing the patient is in a good functional state. As mentioned, this would include resection of operable lesions, especially those causing significant mass effect, and GKRS for smaller mets, or for those located in deeper, more eloquent regions of the brain.

Concomitant with this strategy is simultaneous aggressive treatment of non-CNS systemic disease which is virtually always present in brain metastasis patients. This generally involves ongoing chemotherapy and/or biologic therapy depending on the disease, with ever more patients achieving improved survival. In this way, even patients with multi-organ metastatic disease can live functionally longer lives, thereby transforming the disease into a more chronic one, rather than the acute, fulminant process which we have been accustomed to managing.

Given this changed paradigm with respect to brain metastasis management, the historic dogma of simply referring all patients to Radiation Oncology is no longer appropriate. A multimodality approach is warranted, with input from Radiation Oncology, Neurosurgery, Medical and Neuro-Oncology and Rehabilitation medicine. With the expert input from these services, an individualized approach can be applied.

Future directions will involve more effective treatment for the still common patient that presents with multiple, large brain metastasis and/or extensive systemic disease. New and improved systemic agents, including those which can reliably cross the blood brain barrier are being developed, with drugs such as Temozolamide (Temodar™) already making an impact in clinical practice.

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