Brain metastases
WEIGHING FUNCTIONAL AND PROGRESSION ADVANTAGES

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TRIAL SUMMARY: Whole brain radiation added to radiosurgery
Brown PD. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. ASCO 2015. J Clin Oncol 33, 2015 (suppl; abstr LB44)

In a plenary session at ASCO 2015, Brown et al. presented the results of Alliance NCCTG N0574, a phase 3 trial comparing whole-brain radiation therapy (WBRT) plus radiosurgery (SRS) to SRS alone in patients with 1 to 3 brain metastases, each <3 cm, by contrast magnetic resonance imaging (MRI). The primary endpoint was cognitive progression (CP), defined as decline >1 standard deviation (SD) from baseline in any of the 6 cognitive tests conducted at 3 months. A total of 213 patients were enrolled, with 2 ineligible and 3 cancels prior to receiving treatment. Cognitive progression at 3 months was more frequent after SRS+WBRT vs SRS alone (88.0% vs 61.9% respectively, p=0.002). There was more deterioration in the SRS+WBRT arm in immediate recall (31% vs 8%, p=0.007), delayed recall (51% vs 20%, p=0.002), and verbal fluency (19% vs 2%, p=0.02). Intracranial tumour control at 6 and 12 months were 66.1% and 50.5%, respectively, with SRS alone vs 88.3% and 84.9%, respectively, with SRS+WBRT (p<0.001). Differences in median overall survival (OS) were statistically nonsignificant at 10.7 months for SRS alone vs 7.5 months for SRS+WBRT respectively (HR=1.02, p=0.93).

COMMENTARY: A significant number of Canadian cancer patients are affected by brain metastases. For instance, of 231,397 patients who died of cancer in Ontario between 1998 and 2007, 13,944 received at least 1 course of palliative brain radiation therapy (RT) in the last 2 years of life (6.0%). Approximately 10% to 20% of patients with cancer are eventually diagnosed with brain metastasis, with lung cancer, breast cancer and melanoma representing the most common tumour sites of origin. Previously, the practice of adding WBRT to SRS has varied across cancer centres, due to differences in physician experience and expertise, availability of equipment, as well as the suboptimal quality of available evidence in the literature to guide therapy.

The Alliance trial, not surprisingly, demonstrated that the cognitive progression is worse in the WBRT+SRS arm, thereby meeting the trial’s primary endpoint. The trial also suggests that the treatment of micrometastases with the addition of WBRT to prevent intracranial relapse may not translate into an OS benefit. Given that the trial was underpowered to assess the secondary endpoint of survival, a larger confirmatory trial is needed to confirm this finding. On the other hand, a 2012 Cochrane systematic review of 2 previous trials evaluating the same hypothesis also suggested a lack of survival benefit and an improved cognitive function with SRS alone. A recent individual patient data meta-analysis that included 3 trials and 364 of the pooled 389 patients showed that, for patients ≤50 years of age, SRS alone favoured a survival benefit, and the initial omission of WBRT did not impact distant brain relapse rates. However, this meta-analysis was limited by a small number of trials and patients. As such, a further meta-analysis incorporating the Alliance trial data might be worthwhile to improve the statistical power.

SRS is not uniformly available in all cancer centres, or even to all centres with radiation oncology expertise, which presents an important barrier to patient access. Due to the setup and infrastructure costs, the technical expertise required for SRS planning and the interdisciplinary nature
of CNS metastasis management, SRS services are typically centralized in academic tertiary cancer centres in Canada. Further data are needed to examine the effect of the distance to SRS centres on accessibility. Studies in British Columbia have demonstrated that the distance to radiation oncology centres is inversely proportional to patient access to palliative radiotherapy.12 Another key question relates to the magnitude of benefit that SRS offers compared with WBRT alone. For example, the RTOG 9508 trial showed that WBRT+SRS improved OS compared with WBRT alone in patients with 1 brain metastasis but not in those with 2 or 3; however, in patients with favourable prognosis, as determined by the graded prognostic assessment (GPA), there may be a survival advantage with WBRT+SRS regardless of whether the patient had 1, 2, or 3 brain metastases.10,11 Certainly, WBRT is simpler to deliver, and more widely available in smaller cancer centres. A potential area of future research would be to better determine which groups of patients benefit most from SRS over WBRT.

The economic impact of brain radiotherapy is complex. One study showed that the average cost of SRS alone to be $119,000 vs $74,000 for the SRS+WBRT arm, due to the increased risk of subsequent CNS relapse in the SRS arm.12 Another study showed that OS and utility scores in the SRS alone group were significantly higher than for the SRS+WBRT group among randomized patients while neither metric was statistically different in the nonrandomized cohort.13 The incremental cost-effectiveness ratios (ICER) of SRS alone over WBRT+SRS were $47,201, $74,560, and $56,455 per QALY for randomized patients, nonrandomized patients and all patients, respectively. Sensitivity analysis demonstrated that the likelihood of having 1 vs 2 to 3 brain metastases had the highest impact on ICER. In other words, patient selection and posttreatment surveillance, as well as subsequent treatments of brain relapse, will affect the overall cost effectiveness. The economic analysis does not take into account the potential patient anxiety associated with a surveillance strategy, or symptoms and morbidity associated with CNS relapse. Currently, there is no evidence to guide us in this process post radiation therapy, and further studies are needed.

In summary, many patients with metastatic cancer are affected by brain metastasis. The Alliance study presented at ASCO 2015 suggests that SRS may produce comparable survival outcomes without treatment of the whole brain (i.e. WBRT), improving preservation of cognitive function in patients with 1 to 3 brain metastases. While the study is hypothesis generating, the optimal treatment of brain metastases in different subsets of patients remains unclear in terms of efficacy, cost effectiveness and accessibility of different treatment modalities.

References