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Prognostic Factors for stereotactic radiosurgery-treated patients with cerebral metastasis: Implications on randomised control trial design and inter-institutional collaboration

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Abstract ***Introduction:*** Defining key prognostic factors for patients with cerebral metastases who underwent stereotactic radiosurgery (SRS) treatment will greatly facilitate future clinical trial designs.

Methods: We adopted a two-phase study design where results from one cohort were validated in a second independent cohort. The exploratory analysis reviewed the survival outcomes of 1017 consecutive patients (with 3610 metastases) who underwent Gamma radiosurgery at the University of California, San Diego (UCSD)/San Diego Gamma Knife Center (SDGKC). Multivariate analysis was performed to identify prognostic factors. Results were validated using data derived from 2519 consecutive patients (with 17,498 metastases) treated with SRS at the Katsuta Hospital.

Results: For the SDGKC cohort, the median overall survival of patients following SRS was 7 months. Two year follow-up data were available for 85% of the patients. Multivariate analysis found that patient age, Karnofsky Performance Status, systemic cancer status, tumour

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histology, number of metastasis and cumulative tumour volume independently associated with overall survival ($p < 0.001$). All statistical associations were validated by multivariate analysis of data derived from the Katsuta Hospital cohort.

Conclusions: This is the first integrated study that defined prognostic factors for SRS-treated patients with cerebral metastases using an inter-institutional validation study design. The work establishes a model for collaborative interactions between large volume centers and provides prognostic variables that should be incorporated into future clinical trial design.

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1. Introduction

Management of patients with cerebral metastases remains a major challenge in neuro-oncology. Metastatic tumours to the cerebrum constitute one of the most common oncologic conditions of the adult central nervous system [1,2]. Though the exact incidence of cerebral metastases remains unknown, estimates suggest that up to 10% of all cancer patients will develop cerebral metastases during their clinical course [3]. Moreover, the incidence of cerebral metastases is projected to increase in the upcoming years [4]. Thus, addressing management issues related to cerebral metastases is of critical importance.

Radiation has widely been accepted as a primary modality of treatment for cerebral metastases [5]. Randomised controlled trials (RCT) have shown that whole brain radiation therapy (WBRT) increases the median survival in patients afflicted with cerebral metastasis by 3–6 months [6,7]. This therapeutic effect is unmatched by the other adjunctive modalities, including surgery [8]. The development of stereotactic radiosurgery (SRS) as a platform for radiation delivery has raised the controversy as to whether WBRT is necessary [9]. The controversy involves whether patients with limited number of brain metastasis should undergo WBRT or focal radiation (SRS) delivered only to the radiographically visible tumours.

The resolution of this fundamental question will require thoughtful clinical trials with randomised design. A major challenge in the design of such trials is that cerebral metastasis is an umbrella term that captures a highly heterogeneous population of patients with differing underlying patho-physiologies [10]. In order to advance treatment paradigms for patients with cerebral metastasis, efforts must be made to identify more homogenous disease populations. We propose that this goal can be achieved by identifying prognostic variables that proxy the underlying patho-physiologies, selecting the patient populations pertinent to the question at hand and randomising only these subsets of patients [11].

A number of prognostic factors have been proposed for patients suffering from cerebral metastases, including age [12,13], Karnofsky Performance Status (KPS) [13,14], systemic cancer status [14,15], tumour histology [16], number of metastasis [17,18] and cumulative tumour volume [19]. However, there are conflicting results in the relative importance of these variables [20]. For instance, in the initial landmark work that defined the prognostic importance of age, KPS and systemic cancer status [13], primary tumour site did not appear to correlate with overall survival. Yet, there are a number of other studies [18,21–23] documenting that breast cancer patients with cerebral metastases exhibit improved survival. Similarly, there are significant discrepant results pertaining to the importance of cumulative tumour volume relative to the total number of metastases [18,19,24–29]. In order to move the field forward and to afford opportunities for intelligent clinical trial design, there is a critical need to perform an integrated analysis of the various proposed prognostic factors.

To this end, we retrospectively analysed our data set of 1017 consecutive patients who underwent radiosurgery for 3610 cerebral metastasis. We found independent prognostic value in all previously reported variables, include patient age, Karnofsky Performance Status, systemic disease status, tumour histology, the number of cerebral metastases and the cumulative volume of cerebral metastases. We validated our findings using another cohort of 2519 patients who underwent radiosurgery for 17,498 cerebral metastasis at the Katsuta Hospital. Future randomised trials should incorporate these variables in terms of study design.

2. Methods

2.1. Patient selection

For the initial exploratory analysis, we performed an Institutional Board Review (IRB) approved retrospective review of consecutive gamma knife SRS-treated patients for indication of cerebral metastases. The review period spanned 1994 to 2011. 1017 patients with the five most common types of cerebral metastasis (breast, lung, colon, melanoma and renal) were included in this analysis. Each patient had been referred for radiosurgery by a neurosurgeon or radiation oncologist. Data collected from the in-house electronic medical record system included age, gender, KPS, primary tumour pathology, number of metastases, volume of each tumour, history of prior radiation treatment and the last date of follow-up. We accessed the Social Security Administration Master Death Files [30] to obtain dates of all patient deaths. The validation dataset was

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