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The number of prior lines of systemic therapy as a prognostic factor for patients with brain metastases treated with stereotactic radiosurgery: Results of a large single institution retrospective analysis

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ABSTRACT

Objectives: It is presently unknown whether patients with brain metastases from heavily pre-treated cancers have a significantly different prognosis than those with less pre-treatment. In this study we sought to identify whether the number of prior lines of systemic therapy are associated with clinical outcomes in patients with brain metastases who received stereotactic radiosurgery (SRS).

Patients and Methods: Between July 2000 and July 2017, 377 patients with brain metastases were treated with upfront SRS. We performed a large, single institution retrospective analysis of these patients. Kaplan Meier analysis was used to estimate survival times. Competing risk analysis was used to estimate times to local failure (LF) and distant brain failure (DBF). Multivariate analysis was performed to estimate the hazard ratios (HRs) for overall survival (OS), neurologic and non-neurologic death for patients with 1, 2 and 3+ lines of prior systemic therapy.

Results: Of the 1077 patients with brain metastases treated with SRS, 377 received prior systemic therapy with a median of 1 (range: 1–9) lines of prior therapy. Median OS was 8.70 months (95% CI, 7.9–9.5). Median OS for patients with 1 prior line of therapy, 2 prior lines of therapy and 3 or greater lines of therapy were 9.93-, 9.05-, and 6.18-months, respectively (log rank p = .04). Lines of therapy as a continuous variable was not associated with LF or DBF on competing risk analysis. The percentage of patients that died of neurological death was 36%. Greater prior lines of therapy (1 vs. 2 vs. 3 and greater) was associated with a greater likelihood of dying of non-neurologic death (gray's p = .01), but was not associated with likelihood of dying of neurologic death (p = .57).

Conclusion: Lines of therapy are associated with OS and non-neurologic death but are not associated with neurologic death, LF or DBF.

1. Introduction

Stereotactic radiosurgery (SRS) has become the standard of care for patients with four or fewer brain metastases given the results of recent randomized trials [1,2]. However, beyond four metastases, there is less compelling data for use of SRS alone as opposed to whole brain radiotherapy (WBRT) [3]. As such, the use of prognostic factors other than the number of metastases can still be quite helpful in clinical decision-making for patients with brain metastases.

The number of lines of prior therapy a patient has previously received may be able to serve as a surrogate marker for how heavily pre-treated their cancer is, and has been shown to yield prognostic information in various types of cancer in the past [4,5]. It may be that patients who have had multiple lines of therapy are at a later point in their natural history - making their expected survival less due to having fewer remaining systemic options and less biologic reserve.

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Heavily pre-treated cancers generally demonstrate worsening responses to further lines of chemotherapy. Various escape mechanisms such as removal of chemotherapy from cancer cells [6] and an increase in the population of resistant cancer stem cells [7] have been described. There is little known on how these resistant clones affect patient outcomes after SRS for brain metastases, particularly given a different mechanism for tumor cell kill.

The present series represents a single institutional retrospective analysis of patients with brain metastases treated with upfront SRS with the intention of assessing the role of prior systemic pre-treatment as a potential prognostic factor with regards to endpoints of survival, patterns of intracranial progression and cause of death.

2. Patients and methods

2.1. Data acquisition

This study was approved by the Wake Forest Institutional Review Board. Patients were identified from the Wake Forest Gamma Knife Database, which was searched for patients who had undergone upfront SRS without prior WBRT. Patient characteristics such as age, sex, lowest SRS dose, number of brain metastases at the time of first Gamma Knife (GK), status of systemic disease, and extent of systemic disease were determined through the electronic medical records. Status of systemic disease was defined as either stable or progressive as previously described [8]. Extent of systemic disease was defined as none, oligometastatic or widespread as previously described [8]. Patient characteristics are summarized in Table 1. The primary diagnoses and relevant histologies are summarized in Table 2.

2.2. Stereotactic radiosurgery

Patients were evaluated for radiosurgery by a team consisting of a radiation oncologist and a neurosurgeon. Patients were treated on the Leksell Model C unit before May 2009 and the Leksell Perfexion unit after May 2009. Treatment was performed on the GammaPlan treatment planning system (Elekta, Stockholm, Sweden). A median minimal dose of 20 Gy (IQR: 17–22) was generally prescribed to the 50% isodose line at the margin of each metastasis. Dose prescription was based on guidelines published by Shaw et al [9].

Table 1
Patient Characteristics.

Sample size	377	
Age at 1st GK (median [IQR])	60.9 [53.2, 68.1]	
Gender (%)	Female	215 (57.0)
	Male	162 (43.0)
Lowest SRS dose (median [IQR])	20 [17,22]	
Metastases at 1st GK (median [IQR])	2.00 [1.00, 3.00]	
Extent of disease (%)	None	43 (11.4)
	Oligometastatic	130 (34.5)
	Widespread	174 (46.2)
	Unknown	30 (8.0)
Status of systemic disease (%)	Stable	222 (58.9)
	Progressive	106 (28.1)
	New	19 (5.0)
	Unknown	30 (8.0)
Number of Lines of Systemic Therapy Prior to SRS	1	207 (19.2)
	2	76 (7.1)
	3	46 (4.3)
	4	24 (2.2)
	5	10 (0.9)
	6	9 (0.8)
	7	3 (0.3)
	8	1 (0.1)
	9	1 (0.1)

Table 2
Primary Diagnosis and Histology.

Lung (%)	169 (44.8)
Adenocarcinoma (%)	90 (59.6)
NSCLC NOS (%)	45 (23.4)
SCC (%)	28 (15.0)
SCLC (%)	6 (2.0)
Breast (%)	83 (22.0)
Hormone receptor positive (%)	40 (46.1)
Her2+ (%)	28 (32.8)
Triple negative (%)	7 (10.9)
Triple positive (%)	4 (3.9)
Her2 status unknown (%)	4 (6.3)
Melanoma (%)	40 (10.6)
BRAF+ (%)	8 (19.1)
BRAF- (%)	2 (6.6)
unknown (%)	30 (74.3)
GI (%)	31 (8.2)
Colorectal (%)	23 (69.0)
Esophageal (%)	7 (25.3)
Other (%)	1 (5.7)
Renal (%)	30 (8.0)
GYN (%)	10 (2.7)
Sarcoma (%)	2 (0.5)
Other (%)	12 (3.2)

2.3. Definition of lines of therapy

A line of therapy was defined as a systemically administered therapy such as cytotoxic chemotherapy, hormonal therapy, immunotherapy or targeted agent that was delivered to treat a new diagnosis of cancer or a cancer recurrence. A new line of therapy was determined based on a change of therapy for disease progression or recurrence or an intolerable adverse toxicity from a prior line of therapy [10].

2.4. Patient follow-up and response assessment

Patients were followed clinically and with an MRI of the brain 4–8 weeks after initial SRS. Subsequent visits were generally every three months for the first two years, and then were spaced out less frequently after that. Distant brain failure (DBF) was defined as a new lesion within the brain that was outside of the prior radiosurgical target dose. Local failure (LF) was defined by either surgical pathology or imaging evidence of a 25% increase in the region of enhancement on an MRI axial slice along with increased perfusion on perfusion-weighted imaging as previously reported [11]. Neurologic death was defined as previously reported by McTyre et al [12].

2.5. Statistics

Median follow-up and time-to-event outcomes were defined beginning at the time of SRS and extending to the time of most recent follow-up or to the event of interest. Overall survival (OS) outcomes were summarized using the Kaplan-Meier method, with log-rank tests performed for outcomes stratified by lines of therapy. Cox proportional hazards models were created for each predictor variable for OS, and multivariate Cox models were then created using known predictors of OS as well as lines of therapy. Cumulative incidences were estimated for DBF and LF, with Gray's tests performed for outcomes stratified by lines of treatment. Competing risks models were developed to determine the single variable subdistribution hazard ratios (HR) associated with each predictor for each of these events. Patients with no prior lines of therapy were excluded from the analyses assessing for role of numbers of lines of therapy because untreated patients are considered to be a heterogeneous population with some patients having aggressive disease that has metastasized early in the natural history [13], and others with non-aggressive disease. Statistics were performed using R version 3.4.0