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Tracking Growth of Brain Metastases

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Tracking the Growth of Brain Metastases

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Background: Literature is relatively sparse on the growth rate of brain metastases. This is an important concept, given that the time delay between imaging and treatment may result in clinically significant tumor growth that could alter treatment planning. Understanding the growth rate of brain metastases is also useful in determining the value of radiation therapy for poor performance patients. This study will potentially shed light on this subject and spur further research.

Methods: This qualitative study includes 21 patients treated with Gamma Knife therapy at MD Anderson of Cooper University Hospital. These 21 patients had various amounts of brain metastases, totaling 38 metastases. All patients had never received SRS or chemotherapy in the past or during the timeframe between imaging to treatment. All patients had 2 MRI imaging sets. Imaging sets were retrospectively reviewed to measure volume, size of greatest dimension, and type of lesions.

Results: By size of greatest dimension, our data for all masses revealed a growth rate of 0.12mm/day (SD ± 0.23). solid lesions at 0.12mm/day (SD ± 0.17), necrotic lesions at 0.13mm/day (SD ± 0.25), and cystic lesions at 0.05mm/day. When studying growth rate in volume, all masses had an average growth rate at 0.03mL/day (SD ± 0.06), solid lesions at 0.02mL/day (SD ± 0.07), necrotic lesions at 0.04mL/day (SD ± 0.04), and cystic lesions at 0.02mL/day.

Conclusion: Our results show growth between imaging sets that may have clinical significance for SRS treatment planning. Further research should be done into this subject to optimize delivery of radiation treatment.

Introduction

Brain metastases are the most common type of intracranial tumor in adults, occurring with much greater frequency than primary brain tumors.[1] Evidence suggests that the incidence of brain metastases may be increasing, although this could be secondary to a larger elderly population and more advanced imaging modalities leading to greater detection.[2] There is also evidence that advances in chemotherapy may be responsible for the increased incidence of brain metastases, as these tumors may only become clinically apparent after a patient's life is prolonged via chemotherapy.[2] In adults, the most common primary malignancies in those with brain metastases include lung cancer, followed by melanoma, renal, breast, and colorectal cancers.[3]

Hematogenous spread is the most common route of delivery from site of primary malignancy to the brain.[4] After traveling through the blood, cancer cells most often deposit at the gray and white matter junction.[5,6] The distribution of brain metastases positively correlates with the amount of blood flow. This results in most brain metastases residing in the cerebral hemispheres, followed by the cerebellum and brainstem.[5,6] For unknown reasons, some primary malignancies tend to metastasize in particular regions of the brain.[5,6]

It is difficult to determine the precise incidence rate of brain metastases. While it is estimated that approximately 21,000 to 43,000 patients are diagnosed each year with brain metastases using census data, autopsy suggests that the incidence rate may lie over 100,000.[7] This discrepancy may be due to the variability in symptomatology in those with brain metastases, allowing many to go undiagnosed. [7] Many different statistical models have been developed to help determine the incidence rate, however no universal consensus has been reached.[7]

Brain metastases can cause a large variety of clinical presentations, from mild to devastating. This can include headache, neurologic deficits, cognitive dysfunction, seizures, and stroke.[6,8] Headache is the most common presentation, and typically presented as a tension headache.[9] This often presented with other symptoms, such as worsening with position and nausea and vomiting.[9] Although early morning headaches are more specific for brain tumors, they are much less common.[9]

Mortality in those diagnosed with brain metastases is high. Hall et al's[10] research was aimed at determining the incidence of long-term survival for patients with brain metastases (defined as ≥2 years). They compared long-term survival between varying primary cancers. They found that the long-term survival rate in these patients was dependent on their primary cancer type.[10] Of note, only 18% of patients died of central nervous system progression, while 57% died of systemic disease progression.[10] This demonstrates that most patients with brain metastases do not die from these lesions themselves, and this is important when determining management for poor performance patients.

Magnetic resonance imaging (MRI) has become the predominant imaging modality to diagnose brain tumors.[6,11,12] While computed tomography (CT) scan and non-contrast MRI can be used, they are not as sensitive as contrast-enhanced MRI.[6,11,12] When contrast-enhanced MRI is used, brain metastases can often be distinguished from other types of brain tumors, which ultimately helps to determine the next step in management.[6,12] Defining characteristics of brain metastases include: multiple tumors, distribution at the junction of the grey and white matter, circumscribed margins, excess vasogenic edema surrounding the tumor.[6] If it is too difficult to establish a clear diagnosis of brain metastasis through imaging, biopsy can be performed.[6] If brain metastasis is proven through biopsy and the primary tumor is not known, it is most prudent to investigate the lung, since lung cancer is the most common primary tumor producing brain metastases in the United States.[6]

Multiple treatment modalities have been established for the treatment of brain metastases, including chemotherapy that readily crosses the blood-brain barrier, Gamma Knife and Cyberknife (both of which fall under the umbrella term stereotactic radiosurgery), whole brain radiation therapy (WBRT), and neurological surgery.[13] Gamma Knife and Cyberknife offer a strong and focused dose of radiation to specific areas of the brain, minimizing the damage to surrounding structures and minimizing neurological complications.[13] This tends to be more beneficial when metastases are clearly identifiable and are not too numerous.[13] WBRT is useful when there are numerous brain metastases, with many that are likely present but unable to be clearly identifiable on imaging. WBRT increases the risk of neurologic complications relative to stereotactic radiosurgery, as it is not as specific in its administration of radiation when

compared to SRS.[13] However, because it acts more diffusely, it can provide radiation to multiple brain metastases both seen and not yet seen on imaging.[14]

There is strong evidence supporting the use of stereotactic radiosurgery for brain metastases. For example, Magnuson et al's[15] research on the appropriate time to use radiation therapy relative to chemotherapy treatment supports the use of early radiation therapy. Their study analyzed 202 patients who were diagnosed with non-small cell lung carcinoma (NSCLC) and found to have an epidermal growth factor receptor (EGFR) mutation. Their results suggested that the deferral of local radiation therapies in patients with NSCLC and EGFR mutation receiving tyrosine kinase inhibitors (TKI) had inferior overall survival compared to patients who received local radiation therapy and TKI upfront.[14]

SRS is largely dependent on imaging to guide treatment decision-making. While abundant research has been done on these different modalities, literature is relatively sparse on the growth rate of brain metastases. This is important, given that the time delay between imaging and delivery of treatment may result in clinically significant tumor growth that could alter treatment planning.

This study of growth rate in brain metastases is particularly relevant in therapies such as Cyberknife, where treatment planning may be based on imaging obtained >1 week before treatment administration. This contrasts with Gamma Knife therapy, where a pretreatment MRI is always obtained within hours of treatment. The understanding of growth rate in brain metastases can increase the confidence of radiation oncologists on the effects of delay in treatment, and potentially provide ways in which they can compensate and account for tumor growth during this time frame, such as a compensatory increase in the treatment margins surrounding the brain tumor.

As of this time, there are no current recommendations for imaging to treatment delay. Seymour et al's[16] research attempted to determine the length of time from imaging to treatment that is appropriate. This study included 82 patients and 151 brain metastases evaluated for. They found that local freedom from progression (LFFP) remained significantly lower for lesions with a delay in treatment from imaging at a period of ≥14 days.[16] They described that ideally the treatment delay would be less than 14 days,

however, at this time this works as a starting point in determining the optimal delay in radiation treatment.[16]

Understanding the growth rate of brain metastases is also useful in determining the value of radiation therapy for poor performance patients. For example, a patient with brain metastases who has a poor prognosis may not benefit from radiation therapy if it is determined that their tumor growth will not be significant in their lifetime. This may provide an improved quality of life (QOL) for those patients who otherwise may have suffered from complications of radiation therapy.

We hypothesize that the masses will not outgrow a 2-mm expansion of margins from initial diagnostic MRI to pre-treatment (Gamma knife) MRI. Patients who received Gamma Knife therapy were chosen to be reviewed given the necessity of requiring 2 MRI imaging sets prior to treatment: 1 set at diagnosis and a 2nd imaging set pre-treatment, which allowed for simple and consistent comparison. Our goals of the study are also to determine a general growth rate for brain metastases to address the aforementioned uncertainties of delay of treatment and determine the value of radiation therapy in poor performance patients.

Methods

This study includes 21 patients treated with Gamma Knife therapy at MD Anderson of Cooper University Hospital throughout years 2015-2016. These 21 patients had varying amounts of brain metastases, with a total of 38 metastases. All patients had never received SRS in the past or during the timeframe between imaging to treatment. No patients were receiving chemotherapy during this timeframe. All patients, excluding one, had 2 imaging sets: 1 diagnostic MRI and 1 pre-Gamma Knife therapy MRI. One patient had a total of 3 imaging sets due to a large delay in receiving radiation treatment after diagnosis, necessitating a repeat MRI. All MRI imaging results were reviewed using Pinnacle software.

Size of greatest dimension was measured for each tumor on diagnostic MRI and pre-treatment MRI. Size of volume was also measured. This was mainly performed by one researcher to maintain

consistency in measurements, with collaboration only on difficult cases to ensure accuracy of measurement.

A 2-mm expansion was also placed around each tumor in diagnostic MRI. This 2-mm expansion was then viewed on the pre-treatment MRI to determine if the lesion had outgrown the expansion. This was to observe if enough coverage could be attained with expansion of the lesion on diagnostic MRI to base adequate radiation treatment on.

Results

The mean number of brain metastases observed per patient in this study was 1.69 (SD ± 1.17) lesions. 8 of the patients observed had multiple metastasis on MRI, while the others had 1 singular lesion. The patient with the most brain metastases studied had a total of 6 lesions.

MRI images were analyzed using Pinnacle software, and the types of tumors were classified as either being solid, cystic, or necrotic. 24 of the lesions observed were solid, making up 64.1% of tumors observed. 13 lesions were necrotic, making up 34.2% of tumors observed. 1 lesion was cystic, making up 2.63% of tumors observed. Table A includes our collected data for each type of tumor.

Our collected data had a mean time span from diagnostic MRI to pre-treatment MRI of 20.39 days (SD ± 16.54). In this time, the size of greatest dimension increased from a mean of 1.23cm (SD ± 0.73) to a mean of 1.45 (SD ± 0.71). In volume, masses grew from a mean of 1.27mL (SD ± 1.92) to a mean of 1.92 (SD ± 2.66).

For solid brain metastases specifically, we calculated a mean time span from diagnostic MRI to pre-treatment of MRI of 15.88 days (SD ± 6.33). In this time, in solid masses we observed a change in the mean size of greatest dimension of 0.69cm (SD ± 0.69) to a mean of 1.27cm (SD ± 0.73). In volume, solid masses grew from a mean of 1.12mL (SD ± 2.17) to a mean of 1.47mL (SD ± 3.00).

For necrotic brain metastases specifically, we calculated a mean time span from diagnostic MRI to pre-treatment of MRI of 28.46 days (SD ± 25.58). In this time, in necrotic masses we observed a change in the mean size of greatest dimension of 1.46cm (SD ± 0.79) to a mean of 1.74cm (SD ± 0.60). In volume, necrotic masses grew from a mean of 1.44mL (SD ± 1.62) to a mean of 2.71mL (SD ± 1.86).

In our sample population, we only observed one lesion that we characterized as cystic. The timespan between diagnostic MRI to pre-treatment MRI was 24 days. In this time, the cystic lesion developed from a size of greatest dimension of 1.87cm to 1.74cm. In volume, the cystic mass developed from 1.99mL to 2.39mL.

Growth rates were calculated for the total of these metastases. When studying the size of greatest dimension, the average rate of development for all masses was 0.12mm/day (SD ± 0.23). When studying the total volume of each mass, the average rate of development for all masses was 0.03mL/day (SD ± 0.06).

Growth rates were also calculated for individual types of metastases, including the distinctions of solid, necrotic, and cystic. Solid lesions were represented the most, as 24/38 (64.1%) of our lesions were designated as solid during review of images. By size of greatest dimension, solid lesions developed at an average rate of 0.12mm/day (SD ± 0.17). By volume, solid lesions developed at a rate of 0.02mL/day (SD ± 0.07).

Necrotic lesions were the second most common brain metastases in this study, making up 13/38 (34.2%) of the lesions observed during review of imaging. By size of greatest dimension, necrotic lesions developed at an average rate of 0.13mm/day (SD ± 0.25). By volume, necrotic lesions developed at a rate of 0.04mL/day (SD ± 0.04).

Only one cystic lesion was studied included in our sample population. This cystic lesion represented 1/38 lesions (2.6%) of tumors observed, vastly less than the other types observed in this study. This lesion grew at an average rate of 0.05mm/day by size of greatest dimension. By volume, this lesion grew at an average rate of 0.02mL/day.

Expansion of margins was performed using diagnostic MRIs, and then compared with pre-treatment MRI to observe extent of coverage. Of the lesions observed, 20 of the 38 masses, or 52.63%, would be covered on pre-treatment MRI by a 2-mm expansion of diagnostic MRI lesion margins over the average of 20.39 days (SD ± 16.54).

Discussion

Of the results obtained in this study, perhaps the most important is the percentage of lesions covered with 2-mm expansion of margins 20.39 days (SD ± 16.54). 52.63% is concerning, particularly for patients who require Cyberknife since these plans may be determined >1 week in advance, unlike Gamma Knife where treatment plans are determined from a pre-treatment MRI immediately before therapy. This proved our null hypothesis to be incorrect and showed that many lesions did outgrow their 2-mm expansion of margins between imaging sets. This growth is an important measure to quantify in patients undergoing Cyberknife therapy to improve the confidence of radiation oncologists in their treatment plans and ensure adequate coverage of lesions.

Our research has shown preliminary growth rates for brain metastases and aimed to classify growth rates by type of lesion, including solid, necrotic, and cystic. When looking at our data, the average rate of development for all masses was 0.12mm/day (SD ± 0.23). By total volume of each mass, the average rate of development for all masses was 0.03mL/day (SD ± 0.06). It is difficult at this time to compare growth rates of these different classifications due to the small sample size used in this study. One aspect of our results that is important to discuss is the variability in growth rates observed our research. It is evident that growth rates are not uniform amongst growth rates in even the same classifications of brain metastasis used in this study. This makes the clinical relevance, which is based on predictability and expected growth, difficult to ascertain from our early research.

Despite best efforts, some limitations with this study are present. The most prominent limitation is the small sample size used in this study. Our study included 21 patients that were found to have brain metastases on diagnostic MRI. Brain metastases come from a variety of primary cancer sources, have variable growths, different locations in the brain, different amounts, and variable positioning in the brain. All these factors make it difficult our small sample size of 21 patients to truly assess a general growth rate of brain metastases. A larger sample size could broaden the applicability of this research in provide clinicians with more generalizable approach.

While a broad and general rule for the growth rate of brain metastases would be useful, it would also be optimal to determine an expected growth rate of lesions based on the primary cancer source and type. A larger sample size would also address this, by including enough patients of a specific primary cancer to potentially extrapolate a suspected growth rate. This would enable radiation oncologists to better understand the effects of delay in radiation treatment of different primary cancers. It would also improve the utility of expansion of margins for brain metastases of specific cancers in an evidence-based manner.

In addition to primary cancer types, a larger sample size can also better elucidate the growth rates of different types of brain metastases, specifically solid, necrotic, and cystic distinctions. In the patients observed in our study, there was only one patient with cystic brain metastases. This made it difficult to assess the growth rates of this type of brain lesion. Along with the type of brain metastasis, better understanding of the effect of location on the growth rate would also be beneficial in determining optimal treatment strategy.

Another limitation of this study is the large ranges of data collected. For example, the delay between diagnostic and pre-treatment MRI has great variability in our study. This may be a result of the community served by Cooper University Hospital, where patients often have poor follow-up and thus do not receive timely treatment. The large variability in delay in treatment make it difficult to assess how quickly changes develop in normal settings, where treatment delay is typically $\leq$2 weeks, and often less. A larger sample size may have helped to reduce the variability observed.

Determining margins of the lesions can be a somewhat subjective process and introduce bias. This is another limitation of this study. Efforts were made to minimize the total observers to maintain consistency in results. In some cases, it was necessary to collaborate to determine proper margins. This was particularly necessary in cases where the lesion was not well defined, significant edema was present, or the area of the lesion made it difficult to ascertain proper margins.

Conclusion

This study was important in its' function as a start for research into the growth rate of brain metastases. This is significant for radiation oncology as it may aid in the development of treatment plans for patients, determine which patients (particularly poor performance patients) may not benefit from radiation treatment by using the expected growth as determined by growth rates, and point towards a maximum imaging to treatment delay that has not yet been established.

Our research shows that at 20.39 days (SD ± 16.54), roughly 52.63% of patients were not covered by 2-mm margins. This number is clearly concerning, and treatment delay should be <20 days to ensure prevention of enlargement of brain metastasis and proper margin expansion during treatment planning. The proper treatment delay is still not well-defined, but our evidence adds support to Seymour et al's[16] research that >14 days is likely too long of delay and is detrimental to a patient's survival outcomes.

This research also showed preliminary growth rates of different types of brain metastases. From the data we have collected, it is difficult to ascertain differences in these rates per tumor type due to the small sample size. When looking at the growth rates of the entire body of brain metastases studied, the average growth rate by size of greatest dimension was 0.12mm/day (SD ± 0.23). By volume, this resulted in a growth rate of 0.03mL/day (SD ± 0.06). As discussed, the major limitation of this study is the small sample size. Given the large variability in growth rates between brain metastases, a larger sample size would help to establish greater confidence in the results and narrow the expected growth rate for these lesions, making for greater clinical relevance and predictability.

Areas of future research should be directed towards learning growth rates of brain metastases from different primary sources, an incredibly important criterion for developing a treatment algorithm. This study can function as a starting point for further research in this area. A larger study with a greater sample size will be required to determine more particular rates. After generalizing rates for location of primary cancer, research can be further subdivided into different types of cancer from a given source. For example, brain metastases from non-squamous cell carcinoma (NSCLC) may have a different growth rate if its etiology is an epidermal growth factor receptor (EGFR) mutation. It may also be dependent on cell

type, for example a squamous cell carcinoma versus an adenocarcinoma. It also may depend on the grade of the cancer and the extent of anaplastic changes. Subdividing the growth rates of brain metastases in this function would be more easily applicable and could develop a standardized protocol for determination of treatment planning and margins. The goal would be for an algorithmic approach to determining expected growth over a period of time.

Finally, growth rates could then be further subdivided based on location of lesion. Growth rates may differ for areas of varying vascular supply. Brain metastases are known to distribute in areas of increased vascular supply, likely due to their hematogenous spread, and may grow faster in these areas.[4,5] Certain cancers have been known to metastasize to specific areas of the brain, and a correlation may exist between primary source and vascular supply.[4,5,6]

This is an exciting avenue of radiation oncology research that has the potential to change how care is broadly administered by radiation oncologists. Studying and learning the growth rate of brain metastases may provide answers on reasonable treatment delay and prognosis. It also has the potential to change how poor performance patients are treated to improve quality of life and ensure best care.

Tables and Figures:

Table A:

		All masses	Solid	Necrotic	Cystic
Number of masses		38	24	13	1
Days observed		20.39 (SD ± 16.54)	15.88 (SD ± 6.33)	28.46 (SD ± 25.58)	24
Size of greatest dimension (in centimeters)	Diagnostic MRI	1.23cm (SD ± 0.73)	0.69cm (SD ± 0.69)	1.46cm (SD ± 0.79)	1.87
	Pre-treatment MRI	1.45 (SD ± 0.71).	1.27cm (SD ± 0.73)	1.74cm (SD ± 0.60)	1.74
Size of volume (in milliliters)	Diagnostic MRI	1.27mL (SD ± 1.92)	1.12mL (SD ± 2.17)	1.44mL (SD ± 1.62)	1.99
	Pre-treatment MRI	1.92 (SD ± 2.66)	1.47mL (SD ± 3.00)	2.71mL (SD ± 1.86)	2.39
Growth Rate by greatest dimension (in mm/day)		0.12 (SD ± 0.23)	0.12 (SD ± 0.17)	0.13 (SD ± 0.25)	0.05
Growth Rate by volume (in mL/day)		0.03 (SD ± 0.06)	0.02 (SD ± 0.07)	0.04 (SD ± 0.04)	0.02

Resources

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