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Imaging changes following stereotactic radiosurgery for metastatic intracranial tumors: differentiating pseudoprogression from tumor progression and its effect on clinical practice

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Abstract

Stereotactic radiosurgery has become standard adjuvant treatment for patients with metastatic intracranial lesions. There has been a growing appreciation for benign imaging changes following radiation that are difficult to distinguish from true tumor progression. These imaging changes, termed pseudoprogression, carry significant implications for patient management. In this review, we discuss the current understanding of pseudoprogression in metastatic brain lesions, research to differentiate pseudoprogression from true progression, and clinical implications of pseudoprogression on treatment decisions.

Keywords

Pseudoprogression; Stereotactic radiosurgery; Brain metastases

Introduction

Metastases make up the majority of brain tumor diagnoses, with an incidence of approximately 150,000 to 200,000 new cases per year, though this number appears to be

increasing due to the aging population, improvement in treatment of systemic malignancies, and improved imaging and detection of intracranial metastases [24, 80]. The most common primary tumors include lung, breast, melanoma, renal cell, and colorectal cancers [70].

Stereotactic radiosurgery (SRS) has become standard adjuvant treatment for patients with metastatic intracranial lesions, along with surgery and, at times, chemotherapy. With improvements in the sensitivity of cranial imaging, there has been a growing appreciation for imaging changes, such as transient growth, peritumoral edema, or inflammation following SRS that can be difficult or impossible to distinguish from the imaging findings of true reoccurrence or progression [15, 32]. The significance of this phenomenon, termed pseudoprogression, is not trivial as true progression often requires invasive treatment and results in alterations of the plan for systemic therapy, while pseudoprogression can simply be watched or medically managed if indicated. Notably, further treatment with radiation in this setting is not advised in order to prevent further radiation-induced toxicity. While the mechanism of pseudoprogression remains unknown, it is likely a combination of tumor necrosis, edema, and secondary inflammation that leads to increased vessel permeability. In this review, we report on current literature surrounding pseudoprogression in metastatic tumors and expand on its potential significance in clinical practice.

Historical perspective

Pseudoprogression is primarily reported in patients who underwent radiotherapy for glioblastoma multiforme (GBM) and was first described by Hoffman et al. in 1979. In a study of 51 patients with high-grade glioma, six patients (12 %) had increased computerized tomography (CT) enhancement following radiation, which later disappeared [30]. While the current standard of care includes treatment with radiation and temozolomide, 13–32 % of patients experience a transient increase in their tumor which, following biopsy was not a result of true tumor progression [7, 8, 26, 37, 67, 83]. In patients with GBM, pseudoprogression was often a subacute process and could be distinguished from radiation necrosis, which was more of a late side effect of radiation, occurring 1–3 years following cranial irradiation [4]. Pseudoprogression is not limited to GBM as it has also been described in other primary intracranial tumor types, including vestibular schwannoma and meningioma. While outside the focus of this review, a thorough discussion of pseudoprogression in meningiomas and vestibular schwannomas has been reported [18, 27, 28, 34, 40, 50, 53, 55, 56, 59, 63, 89].

Evidence of pseudoprogression in intracranial metastases

SRS has emerged as one of the primary treatments for patients with intracranial metastases as it is considered both safe and effective [54, 76]. Prior to SRS, surgery and whole brain radiotherapy (WBRT) were the mainstays of treatment for patients with intracranial metastases. However, due to the side effects associated with WBRT, such as neurotoxicity, skin damage, nausea, and vomiting, among others, SRS now represents an often less toxic alternative to WBRT.

In a meta-analysis by Muller-Riemenschneider et al., SRS was compared to WBRT and neurosurgical resection to determine its effectiveness in patients with intracranial metastases

[54]. Patients treated with SRS tended to have improved survival over patients receiving WBRT [16, 43, 64, 65]. When SRS was given with WBRT, there was no survival advantage over SRS alone [2, 3, 13, 38, 57, 72, 75], though there was improvement in mini mental score and a trend toward improved KPS in patients receiving both WBRT and SRS [2]. Four studies compared SRS to neurosurgical resection and WBRT and found that there was no difference in survival [38, 47, 58, 73]. Only a trend toward lower complication rates was seen in patients with SRS [58].

While the abovementioned studies show that SRS was as effective as WBRT and neurosurgical resection, one question that remained unanswered was how best to assess the outcome of this treatment. In 2011, Patel et al. reported that approximately 33 % of intracranial metastases increased in size during follow-up, which was consistent with early reports. Furthermore, increases in lesion size began as early as 6 weeks following SRS and was observed up to 15 months later. The average lesion volume from the initial pre-SRS treatment imaging showed a transient 3.6 and 11.6 % increase at 12 and 15 months post-SRS, respectively. Previously, salvage surgery would have been recommended if an abnormality were noted on at least one fludeoxyglucose positron emission tomography (FDG-PET) or proton magnetic resonance spectroscopy (^1H -MRS). In their experience, 22 of 23 biopsied lesions were consistent with radiation effect and not tumor growth [62].

Radiosensitive tumors (lung or breast) showed the greatest flux in tumor volume with multiple episodes of transient growth over the 36-month follow-up period. Radio-resistant tumors (melanoma, colon, or renal) did not show a transient increase in size as frequently. Kaplan–Meier analysis of this phenomenon found that patients with apparent progression (later determined to be pseudoprogression) following SRS had improved survival as compared to those patients who did not show pseudoprogression of their lesions [62].

Along with tumor histology, the concurrent use of chemo-therapeutics may also contribute to imaging changes following radiation. In a single case report of a patient with eight intracranial metastases for a renal cell carcinoma primary tumor, pseudoprogression was described after treatment with sunitinib and WBRT. The patient was treated to a total dose of 37.5 Gy in 2.5 Gy fractions over 3 weeks and 50 mg of sunitinib once daily for a standard 4 weeks on, 2 weeks off cycle. On day 44 following WBRT, three of the lesions showed an increase in size that had resolved by day 55. Interestingly, sunitinib has been shown to radiosensitize tumors in preclinical models, suggesting a possible interaction between chemotherapeutics and imaging changes following radiation treatment [41, 90].

Imaging modalities to detect pseudoprogression

The standard for monitoring treatment success after SRS is serial magnetic resonance imaging. Because pseudoprogression is indistinguishable from true progression in a single imaging study, it is diagnosed when the imaging progression stabilizes or even resolves over time without further antineoplastic intervention. When evaluated at a single time point, conventional magnetic resonance imaging (MRI) has not been proven to reliably distinguish radiation effect from tumor recurrence [79]. In cases where there is uncertainty regarding

pseudoprogession as compared to true progression after the first 3 months following radiation therapy, patients may be continued on their current therapy and followed closely.

Currently, there is no widely accepted imaging modality that will allow practitioners to detect pseudoprogession on a single imaging session. However, clinical trials aimed at answering the question of the best method to detect pseudoprogession are underway and can be found at the National Institute of Health clinical trials registry (<http://www.clinicaltrials.gov>). While imaging techniques and data supporting various modalities are common in glioma, the various imaging modality studies in patients with intracranial metastases are more limited. Discussed below is data concerning standard MRI, perfusion-weighted MRI, MR spectroscopy, single photon emission CT (SPECT), and PET.

Magnetic resonance imaging

MRI is the standard imaging modality used to detect and follow the progression of intracranial tumors. However, its use in identifying tumor progression versus treatment effect was based primarily on the imaging findings of contrast-enhancement, perilesional edema, necrosis, mass effect, and a heterogenous pattern seen on T2 sequences [19, 21, 23, 25, 33]. Dequesada et al. reported a novel radiographic feature, the lesion quotient, which measures the ratio of the lesion on T2 imaging to the total enhancing area on T1 imaging. They reported that a lesion quotient greater than or equal to 0.6 was seen in all imaging of recurrent tumor and a lesion quotient of 0.3 or less was seen in 80 % of cases of radiation necrosis. The lesion quotient was found to have a sensitivity of 80 %, specificity of 96 %, and negative predictive value of 96 % in patients in which the quotient was <0.3, suggesting that the lesion coefficient is most accurate in identifying radiation necrosis. Similar to many other studies, identifying mixed tumor recurrence and necrosis was less accurate than either recurrence only or necrosis only. Other radiographic features, such as arterio-venous shunting, gyriform lesion and edema distribution, pattern of enhancement, and formation of cysts had low sensitivity and specificity [19]. A follow-up study by Stockham et al. in a larger cohort of patients could not confirm these findings, reporting a sensitivity and specificity for recurrent tumor of 59 and 41 %, respectively. Furthermore, the sensitivity and specificity of treatment effect were 8 and 91 %, respectively [79]. The acceptance of the lesion quotient remains controversial until further studies can confirm an adequate sensitivity and specificity.

A second radiographic feature that can be examined by routine MRI sequences is T1/T2 matching, or the correspondence between the contrast-enhancing volume on T1 sequences and the low-signal defined lesion margin on T2 sequences. Initially reported by Kano et al., this method correlated with tumor progression on histopathology. T1/T2 mismatch, or lack of a defined lesion margin on T2 sequences compared to the lesion margin on T1 sequences, was highly correlated with the treatment effect. Together, the sensitivity and specificity of T1/T2 mismatch for identifying treatment effect was 83.3 and 91.1 %, respectively [39].

Perfusion-weighted MRI

Perfusion-weighted MRI is a technique that can be used to study brain hemodynamics by utilizing the susceptibility effect of intravascular gadolinium within blood vessels. When

this method is used, multiple hemodynamic variables can be obtained, including: relative cerebral blood volume (rCBV) which correlates with tumor microvascular density, relative peak height (rPH) which represents the change in signal following injection of gadolinium, and percentage of signal intensity recovery (PSR), a marker for the integrity of the blood–brain barrier [45, 49].

Because metastatic intracranial tumors are characterized by increased vascularity as well as breakdown of the blood–brain barrier, especially following cranial irradiation, these markers provide an imaging equivalent to the pathological processes occurring at the cellular level. Long reported that the structure of metastatic intracranial tumors' capillaries resembled that of the site of origin, as opposed to capillary structures within the brain [48]. Similarly, Kamiryo et al. reported that capillaries within metastatic tumor were leaky as compared to intact irradiated brain providing a histologic description for meta-static lesions' uptake of contrast [36]. Other histopathological changes, as determined primarily by following failed treatment with radiation, include vascular hyalinization, hemosiderin-laden macrophages, and reactive gliosis [33].

The most commonly studied variable, rCBV is the focus of several studies to differentiate tumor recurrence versus radiation effect. When rCBV, rPH, and PSR were retrospectively studied in 27 patients with enlarging intracranial lesions following Gamma Knife treatment, Barajas et al. reported that these values could reliably differentiate recurrent metastatic tumor from radiation necrosis. They found that the mean, minimum, and maximum PSR values were lower in the cases of recurrent metastatic tumor and that the mean and maximum rCBV and rPH values were significantly higher in patients with recurrent metastatic tumors [5]. Hoefnagels et al. reported that the rCBV component of perfusion-weighted MRI could be used to differentiate progression from radiation effect with a sensitivity of 70 % and a specificity of 100 % when using a cutoff of 2.00 for the tumor rCBV/white matter ratio and 1.85 for the rCBV/gray matter ratio [29]. Similarly, Mitsuya et al. reported that an rCBV ratio >2.1 provided a sensitivity and specificity of 100 and 95.2 %, respectively [52]. Huang et al. also reported that the rCBV component was the best reporter of progression versus radiation effect. They report that an rCBV >2 had a sensitivity and specificity of 56 and 100 %, respectively. Interestingly, they also reported that the best reporter was the increase in lesional size, with a 65 % tumor volume increase, having a sensitivity and specificity of 100 and 65 % for tumor progression, respectively [31].

Magnetic resonance spectroscopy

MR spectroscopy is unique in that it provides data related to the chemical composition of tissues, including glucose, phosphorylcholine/glycerophosphorylcholine (Cho), *N*-acetylaspartate (NAA), lipids (Lip), creatine (Cr), and lactate, among others [20]. While MR spectroscopy was historically used to grade tumors, the individual metabolite levels, as well as their ratios, can be studied as potential markers of tumor recurrence versus radiation effect. ¹H-MRS is the most commonly used method with several studies correlating this imaging with histological findings in both metastatic tumors and glioma [14, 21, 66]. While earlier studies used single voxel techniques, these studies were limited in their ability to differentiate pure radiation necrosis versus partial tumor recurrence [68, 69].

The individual contribution of Cho, NAA, Lip, and Cr to determine tumor progression versus radiation effect has been variable. Cho and Cr are often significantly higher in cases of recurrent tumor because of their role in cellular metabolism. In contrast, treatment effect has been reported to show decreased values of Cho and Cr [74, 81, 82, 88]. However, these values are not fixed, as several studies have shown that their values can flux over time [23, 35]. Interpreting the Lip and lactate levels, and their ability to differentiate tumor recurrence versus treatment effect, have been met with greater difficulty. Lip and lactate are generally not observed in the normal brain but are released under cellular stress, for example, following radiation. The difficulty in interpreting their values arises from the heterogeneity of tumors. Most often, recurrent tumors contain areas of necrosis, limiting the ability for these values to be used independently as biomarkers.

Kimura et al. reported in a series of six patients that ^1H -MRS was able to differentiate progression from recurrence in 100 % of patients [42]. Likewise, in a study of 33 patients, Chernov et al. reported that ^1H -MRS, using multi-voxel spectroscopy, could reliably define pure tumor recurrence, partial tumor recurrence, radiation-induced tumor necrosis, and radiation necrosis of the peritumoral brain using a combination of NAA/Cho and Lip/Cho ratios [10]. Huang et al. reported that the Cho/contralateral brain Cho was the best performing value, with a sensitivity and specificity of 33 and 100 %, respectively [31].

Rock et al. studied the correlation of MRS and histopathology and found that ^1H -MRS could distinguish pure tumor from pure necrosis, using either a Cho/normal Cr ratio or a Lip-Lac/Cho ratio. They were unable to show any marker to reliably distinguish partial tumor recurrence [66].

Single photon emission CT

SPECT is a form of nuclear medicine imaging that allows for three-dimensional reconstructions by imaging from multiple angles. While several radiotracers are available, thallium-201 (^{201}Tl) is the most widely studied in its ability to differentiate tumor progression versus radiation effect. However, its spatial resolution is considerably low. While Kimura et al. reported that ^1H -MRS could reliably distinguish progression versus recurrence in that same study, single photon emission CT with thallium-201 chloride (TlCl-SPECT) was only able to differentiate 67 % of cases [42]. This is similar to results published by Endo et al., who reported that TlCl-SPECT could be used with a positive predictive value of 83.3 % [22]. Serizawa et al. reported the use of SPECT using scatter correction with a triple energy window allowed for better resolution. In that study, they reported a sensitivity of 91 % when using a Tl index >5 to diagnose tumor recurrence versus <3 for radiation injury [71]. While multiple studies have tested this modality for determining progression versus treatment effect, it is primarily limited to patients with glioma and thus is outside the scope of this review [1, 25, 44, 46, 61, 85].

Positron emission tomography

Imaging with PET can be used to determine metabolic activity. The most common agent, FDG, is incorporated into cellular metabolism and is thus a reporter for the increased metabolism seen in regions containing neoplastic tissue. However, due to the high baseline

metabolism of glucose by the brain, the use of FDG to distinguish tumor growth from necrosis has been a significant challenge. Belohlavek et al. reported that FDG-PET was useful in serial studies in patients with initially nondiagnostic MRIs [6].

Other techniques utilize the concept of increased amino acid consumption by neoplastic cells in order to differentiate neoplastic tissue. Comparatively, amino acid tracers are likely superior to FDG as the differential in amino acid metabolism is greater in tumors versus normal brain [12]. Amino acid tracers, including L-methyl- ^{11}C -methionine (11C-MET), O-2- ^{18}F -fluoroethyl-L-tyrosine (^{18}F -FET), and 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) have been reported, primarily in glioma [17, 51, 87]. Tsuyuguchi et al., using 11C-MET PET in a series of 21 patients, reported that analyzing and comparing the mean counts of radioisotope per pixel in suspected tumor (L) versus the normal tissue (N) provided a sensitivity and specificity of 77.8 and 100 %, respectively [86]. Similarly, Terakawa et al. reported that an L/N ratio greater than 1.41 was the best performer in their series of 51 patients, with a sensitivity and specificity of 79 and 75 %, respectively [84].

Other, newer techniques include tumor imaging with ^{18}F -FLT-PET (3-deoxy-3- ^{18}F fluorothymidine). This tracer is unique in that it is not taken up in patients with an intact blood–brain barrier and thus, will only concentrate in a proliferating tumor [11, 77]. A similar agent, ^{18}F 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine, has also been tested for primary diagnosis [9]. Their utility in determining primary tumor recurrence versus radiation effect is, however, currently unknown.

Potential effect of pseudoprogression on clinical practice

Despite the abovementioned evidence, there is currently no imaging nor clinically reliable method for distinguishing pseudoprogression from true progression in patients with metastatic brain lesions that has gained widespread acceptance throughout the oncology community. The result of this is not trivial as mistakenly assuming treatment effect as progression of the underlying malignancy can lead to unnecessary and/or risky interventions.

For example, if pseudoprogression is mistaken for treatment failure, (1) further radiation may be recommended leading to potential catastrophic side effects, including acute encephalopathy, radiation necrosis, and radiation dermatitis; (2) surgery may be recommended despite the inherent risks of anesthesia, infection, and surgical error and/or; (3) systemic therapies, that might still be aiding the patient, might be changed due to the presumption that “progression” is due to failure of systemic chemotherapy (Fig. 1).

Potentially complicating the management of patients with multiple intracranial metastases is the apparent change in size of nonirradiated metastases following stereotactic radiosurgery, termed the abscopal effect. While the mechanism remains unknown, several groups have suggested it to be an immune-mediated phenomenon as a result of disruption of the tumor microenvironment by radiation [60, 78].

The diagnostic algorithm for deciding between conservative management versus a change in treatment in patients with suspected progression should be influenced by the typical

behavior of the underlying pathology. While this might be less difficult to implement in cases of high-grade glioma, following this algorithm in patients with intracranial metastases may prove more challenge. High-grade glioma has a high rate of local recurrence after radiation and often progresses rapidly, suggesting that imaging changes are more likely due to disease progression. In contrast, brain metastases are often successfully controlled by radiosurgery and are more likely to show late imaging changes, with effects often extending out greater than 1 year post SRS, suggesting that the probability of true recurrence and imaging changes may be roughly equivalent.

We recommend that asymptomatic patients with suspected or confirmed pseudoprogression be followed and maintained on their primary adjuvant therapy, including dexamethasone, which may still be effective. Serial MRI studies at more frequent intervals to allow early intervention if there is increasing mass effect or rapid growth are also appropriate.

For serial imaging that is suggestive of continued tumor progression, especially in the setting of increasing neurologic symptoms, surgery should be considered due to its ability to decrease mass effect that is likely causing worsening neurologic symptoms. If there are substantial clinical symptoms, surgery is generally the optimal treatment as it is therapeutic in either situation. If the tumor is truly growing and causing symptoms, resection will remove the active tumor and pathologic confirmation may justify use of additional radiation treatment. However, immediate radiation should be approached with caution, so as not to cause further radiation damage in the case of suspected radiation necrosis. Surgical resection is also therapeutic for radiation injury as symptoms may improve or resolve when the cause of an advancing front of inflammation and/or necrosis is removed.

Special attention to this phenomenon may also be especially important in the care of patients on standard or investigational systemic therapy. We suggest that progression of a brain lesion after radiosurgery not itself be considered a reason to discontinue an investigational systemic therapy if pseudoprogression is likely and neurologic symptoms are not present. In the situation of a progressive brain lesion on experimental or standard therapy, we advocate for continuation of current systemic therapy if it is achieving its goal of disease control elsewhere in the body.

Conclusion

Pseudoprogression is a common imaging finding following SRS for both primary and metastatic intracranial tumors. Imaging technology is still in the early stages of reliably discerning pseudoprogression from true progression. Furthermore, because current investigational imaging protocols are both complicated and expensive, widespread adoption of these technologies has yet to occur. In the setting of pseudoprogression in metastatic intracranial lesions, conservative management is suggested to maintain the patient on a potentially beneficial treatment and to spare the patient from potential side effects of secondary treatments. Furthermore, attention to the possibility of pseudoprogression in the context of clinical trials is paramount in order to report accurate clinical trial results and maintain patients on potentially beneficial experimental treatments.

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Fig. 1.

Suspected progression actually due to pseudoprogression. A 64-year-old female presented with multiple intracranial metastases secondary to primary breast cancer. Her initial diagnosis of breast cancer was made in 2005 and confirmed to be ER+/PR-. In 2010, she developed multiple intracranial metastases and was subsequently treated with WBRT. One year later, multiple new intracranial metastases were found, including **a** one lesion in the left parietal lobe. **b** The patient was treated with SRS at a dose of 1,600 cGy to the 80 % isodose line. **c** Follow-up MRI at 4 months and at **d** 7 months post-SRS showed an increase in lesion size consistent with tumor progression. Due to the onset of neurologic symptoms, the patient underwent a craniotomy for suspected tumor progression. However, intraoperative and final pathology confirmed radiation necrosis without evidence of any viable tumor