QUANTITATIVE MEASUREMENT OF BLOOD-BRAIN BARRIER PERMEABILITY USING PERFUSION-CT IN EXTRA-AXIAL BRAIN TUMORS

A. CIANFONI (1), S. CHA (2), W.G. BRADLEY (3), W.P. DILLON (2), M. WINTERMARK (2)

(1) Università Cattolica del Sacro Cuore (UCSC), Policlinico “Agostino Gemelli”, Department of Radiology, Roma, Italy.
(2) University of California, San Francisco (UCSF) Department of Radiology, Neuroradiology Section, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143-0628.
(3) University of California, Department of Radiology, Neuroradiology Section, San Diego (UCSD).

SUMMARY

Non-invasive assessment of vascular permeability is of main importance in the diagnosis, treatment and follow-up of intracranial tumors. Perfusion-CT is one of the imaging options available, which affords quantitative assessment of cerebral blood volume and blood-brain barrier permeability. Herein we report two cases of extra-axial tumors studied with perfusion-CT. Comparison with perfusion-MRI was available in one case. High permeability values, as measured by perfusion-CT, reflected the absence of blood-brain barrier in these extra-axial tumors.

Key words: perfusion-CT, Brain tumors, extra-axial tumors, permeability, blood-brain barrier.

INTRODUCTION

Assessment of angiogenesis has become a key element in the characterization of brain tumors due to the emergence of anti-angiogenic therapies [1, 2]. Though biopsy and histology remain the gold standard to characterize brain tumor micro-vasculature, the geographic heterogeneity of brain tumors challenges the diagnostic accuracy of this standard approach, and results in a significant rate of sampling errors [3, 4]. Hence, intense research is conducted to develop non-invasive imaging methods affording a comprehensive evaluation of brain tumor vascular supply [5, 6]. One of the approaches proposed is to evaluate the permeability of the blood-brain barrier, which is typically abnormal in the case of tumoral neovessels [7, 8]. This approach has been abundantly investigated using dynamic-susceptibility contrast (DSC) T2*-weighted magnetic resonance imaging (MRI) [9] and dynamic T1-weighted MRI [10, 11]. Ancetotal cases using dynamic perfusion-CT (PCT) have also been reported in the literature [12-14]. The reported cases using PCT were dealing with intra-axial brain tumors only [12-14].

The purpose of this article is to report quantitative measurement of blood-brain barrier permeability, but also of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), obtained using PCT in two patients with extra-axial brain tumors.

CASE 1

A 61-year-old woman known for a metastatic gastric leiomyosarcoma presented to the ER with new onset of headaches and word finding difficulty (figure 1). A multislice CT survey, including non-contrast CT of the brain, PCT, CT-angiography and post-contrast CT of the brain, was performed that allowed to rule out stroke. PCT consisted of two 45-second series with 45 gantry rotations performed in cine mode during intravenous administration of iodinated contrast material. Images were acquired and reconstructed at a temporal sampling rate of 1 image per second, resulting in a series of 45 images for each assessed slice. A total of four slices of 10-mm thickness were obtained.

This CT survey (figure 1) demonstrated a 3-cm round mass, superficially located, deep to the left supra-marginal gyrus. This mass was characterized by intrinsic increased attenuation on the non-contrast CT and by intense enhancement on the post-contrast CT. It was surrounded by moderate amount of vasogenic edema in the adjacent brain parenchyma.
FIG. 1. – 61-year-old woman known for a metastatic gastric leiomyosarcoma presented to the ER with new onset of headaches and word finding difficulty. The initial CT survey demonstrated a 3-cm round mass, superficially located deep to the left supra-marginal gyrus. This mass was characterized by intrinsic increased attenuation on the non-contrast CT and by intense enhancement on the post-contrast CT. It was ultimately demonstrated as a dural metastasis. On perfusion-CT (PCT), this metastasis showed increased cerebral blood volume (CBV), increased cerebral blood flow (CBF), elevated mean transit time (MTT) and very high permeability-surface (PS) product, reflecting the steep slope of the corresponding curve (green) on the Patlak plot derived from the time-density curves. The slope and curve observed in the normal contralateral brain parenchyma are demonstrated in pink (On the Patlak plot, the intercept on the Y axis represents the CBV value, and the slope, the vascular permeability).

Subsequent MRI study showed the metastasis to be relatively hypointense on T2-weighted images and to enhance intensely and homogeneously. On DSC T2* MRI, the mass showed an increased relative CBV compared to the normal-appearing contralateral white matter. Also, the DSC T2* signal curve within the mass showed a lack of return to baseline after the first pass of the contrast bolus, suggesting high vascular permeability and consistent with the interpretation of the PCT Patlak plot.

Fig. 1. – Une patiente âgée de 61 ans, connue pour un léiomyosarcome gastrique métastatique, fut admise aux urgences en raison de soudaines céphalées et de manque du mot. L’examen tomodensitométrique initial met en évidence une masse arrondie de 3 cm, localisée superficiellement dans la région du gyrus supramarginal gauche, hyperdense sur l’examen natif et prenant le contraste sur l’examen suivant l’injection intraveineuse de contraste. Le diagnostic final pour cette masse fut celui de métastase dure. Sur le CT de perfusion (PCT), cette masse est caractérisée par un volume sanguin cérébral (CBV) augmenté, par un débit sanguin cérébral (CBF) augmenté, par un temps de transit moyen (MTT) augmenté et par un produit perméabilité-surface (PS) très augmenté, reflétant la pente raide de la courbe correspondante (verte) sur le graphique de Patlak dérivé des courbes temps-densité. La pente et la courbe observées dans le parenchyme cérébral normal contralatéral sont représentées en rose (sur le graphique de Patlak, l’ordonnée à l’origine sur l’axe des Y représente la valeur de volume sanguin cérébral (CBV), et la pente, la perméabilité vasculaire).
Average cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and permeability-surface product (calculated according to the Patlak model using a Philips Medical System prototype software) measured within the mass were 49.1 \( [\text{cc} \times 100\text{g}^{-1}] \), 72.8 \( [\text{cc} \times 100\text{g}^{-1} \times \text{min}^{-1}] \), 40.4 [sec] and 70.2 \( [\text{cc} \times 100\text{g}^{-1} \times \text{min}^{-1}] \), respectively.

A subsequent MRI study (figure 1) showed the parietal mass to be isointense on T1-weighted images, relatively hypointense on T2-weighted images, with diffusion coefficients comparable to normal-appearing contralateral white matter and no signs of intra-tumoral hemorrhage. The mass enhanced intensely and homogeneously. The post-contrast images demonstrated a dural tail, suggesting a dural origin of the mass. On DSC T2* MRI, the mass showed an increased area over the curve compared to the normal-appearing contralateral white matter, consistent with increased CBV. Also, the DSC T2* signal curve within the mass showed a lack of return to baseline after the first pass of the contrast bolus, suggesting high vascular permeability (figure 1).

The patient underwent surgical resection of the mass that turned out to be a highly cellular dural metastasis of the leiomyosarcoma known in this patient. The high cellularity explained the intrinsic high attenuation on the non-contrast CT and the relatively low T2 signal.

**CASE 2**

A 83-year-old women with known meningiomas presented in the emergency room (ER) with left-sided face, arm and leg weakness of one day duration, following a seizure episode. As in the first patient, a CT survey (figure 2), including non-contrast CT of the brain, PCT and CT-angiography, was performed according to the imaging protocol described above.

The CT survey demonstrated no evidence of acute stroke, but two extra-axial masses, containing calcifications and characterized by heterogeneous enhancement, in the right frontal region and in right parafalcine location, consistent with meningiomas. Hypodensity of the white matter, consistent with vasogenic edema was observed in the adjacent brain parenchyma. Average CBV, CBF, MTT and permeability-surface product were 21.9 \( [\text{cc} \times 100\text{g}^{-1}] \), 65.5 \( [\text{cc} \times 100\text{g}^{-1} \times \text{min}^{-1}] \), 20.0 [sec] and 36.3 \( [\text{cc} \times 100\text{g}^{-1} \times \text{min}^{-1}] \), respectively, in the right frontal meningioma, and 12.4 \( [\text{cc} \times 100\text{g}^{-1}] \), 30.4 \( [\text{cc} \times 100\text{g}^{-1} \times \text{min}^{-1}] \), 24.0 [sec] and 36.3 [cc \times 100g^{-1} \times min^{-1}] in the parafalcine meningioma.

**FIG. 2.** – A 83-year-old women with known meningiomas presented in the emergency room (ER) with left-sided face, arm and leg weakness of one day duration, following a seizure episode. The CT survey demonstrated two extra-axial masses, containing calcifications and characterized by heterogeneous enhancement, in the right frontal region and in right parafalcine location, consistent with meningiomas. On PCT, these meningiomas demonstrated increased CBV and CBF, but also increased PS product. Increased permeability translated on the time-density curves into a large and rapid increase in density within the meningiomas (red and orange curves), without significant return to baseline compared to normal white matter (green curve). On the Patlak plot, increased permeability is responsible for the steep slope of the curves calculated within the meningiomas.

**FIG. 2.** – Une patiente âgée de 83 ans et connue pour des méningiomes fut admise aux urgences en raison d’un hémisyn- drome moteur facio-brachio-crural gauche d’une durée d’un jour, suivi par un épisode de convulsion. L’examen tomoden- sitométrique met en évidence deux masses extra-axiales conte- nant des calcifications et s’imprégnant de contraste de façon hétérogène, localisées dans la région frontale droite et dans la région parafalcine droite, consistentes avec des méningiomes. Sur le CT de perfusion (PCT), ces méningiomes sont caracté- risés par un volume sanguin cérébral (CBV) et un débit san- guin cérébral (CBF) augmentés, mais aussi par un produit perméabilité-surface (PS) augmenté. La perméabilité vascula- laire augmentée se traduit sur les courbes temps-densité par une augmentation rapide et importante des valeurs de densité mesu- rées dans les méningiomes (courbes rouges et oranges), et par une absence de retour à la normale en comparaison avec la substance blanche normale (courbe verte). Sur le graphique de Patlak, la perméabilité augmentée explique la pente raide des courbes calculées au sein des méningiomes.

29.5 [cc*100g-1*min-1], respectively, in the right parasagittal meningioma.

Subsequent brain MRI was performed and confirmed the CT findings, including the absence of reduced diffusion to suggest acute brain ischemia. Comparison with a prior MRI obtained four years before did not demonstrate any significant changes in the size of the two meningiomas and in the extent of the adjacent vasogenic edema. The patient’s initial presentation was considered as consistent with Todd’s paralysis following seizure activity induced by the meningiomas. The patient was discharged home on seizure medication.

DISCUSSION

We report the cases of two patients with extra-axial brain tumors, one with meningiomas and one with a dural metastasis. The measured PCT-derived CBV and permeability-surface products were 21.9 [cc*100g-1] and 36.3 [cc*100g-1*min-1] within the larger right frontal meningioma, and 49.1 [cc*100g-1] and 70.2 [cc*100g-1*min-1] within the dural metastasis. The high CBV values and the high permeability-surface product measured within the dural metastasis correlated with the increased area over the DSC T2* time-intensity curve and the lack of return to baseline after the first pass of the contrast bolus, respectively.

In our cases, vessel permeability was higher in the case of the dural metastasis (70.2 [cc*100g-1*min-1]) than compared to the meningiomas (36.3 [cc*100g-1*min-1]) and when compared to similar measurements obtained for intra-axial tumors, using either PCT (10-40 [cc*100g-1*min-1]) for brain metastases [12], and 7.5 [cc*100g-1*min-1] for glioblastoma multiforme [14], or dynamic T1-weighted MRI (0-13 [cc*100g-1*min-1]) for glial tumors, increasing with their grade [10]. These permeability differences suggest different properties of the vessels supplying intra-axial and extra-axial brain tumors. Glial tumors are supplied by vessels showing relatively preserved blood-brain barrier compared to extra-axial tumors such as meningiomas [15]. This may be related, among other factors, to the vascular supply of glial tumors by internal carotid artery branches, whereas, for meningiomas, and also dural metastases, the supply is mainly through branches from the external carotid artery [16]. Of interest, the perfusion and permeability values observed in the two meningiomas were different from each other, with the right frontal meningioma receiving higher perfusion and showing slightly increased permeability compared to the right parasagittal one. While these differences may be in part accounted for by partial volume averaging effect, they also probably reflect the fact that the vascular supply of meningiomas, and specifically the relative contribution of external and internal carotid artery branches, is variable from one meningioma to the other.

Contrast enhancement is a nonspecific finding, seen with many disorders of the brain. It may correspond to an increased density of vessels, resulting either from formation of very new vessels, from vascular intussusception by the tumor or from recruitment of existing vessels by tumor (vascular cooption), or to an increased permeability of the blood–brain barrier (typically in post-radiation treatment changes), or to a combination of both (in tumors) [14]. The measurement of both CBV and blood-brain barrier permeability with imaging techniques such as PCT permit a separate evaluation of each of these features of neovascularity [10].

Measurement of the blood-brain barrier permeability using PCT and DSC MRI rely on the same mathematical models. One of the frequently used models is the Patlak model [17]. This model describes a method for determining the rate constant of tissue uptake of a tracer from the vascular space using values on tracer concentration in tissue and blood. Practically, it tracks the progressive extravasation of contrast material out of the vessels into the interstitium, by mathematical comparison (deconvolution) of a parenchymal time-signal curve (where there is extravasation) and a reference arterial curve (where extravasation is assumed to be non-significant). The Patlak model typically does not focus on the first pass of contrast material, but considers several passes until equilibrium of concentration between the two compartments is (or tends to be) achieved.

The Patlak analysis leads to graphs such as those represented in figures 1 and 2, where the X-axis describes the time and the Y-axis, a volume typically expressed in [cc*100g-1]. A linear regression is performed from the points calculated by the deconvolution operation. The resulting straight line describes the progressive extravasation of contrast material out of the vessels into the interstitium, with its Y-axis intercept at time 0 corresponding to the CBV (expressed in [cc*100g-1]) and its slope, to the permeability-surface product (expressed in [cc*100g-1*min-1]).

Although the Patlak model is a simplified representation of the reality as a two-compartment model, it is commonly used to determine the tissue uptake of fluorodeoxyglucose during positron emission tomography. Variations on the Patlak analysis have been applied to data derived from perfusion-CT to determine the rate constant of passage of contrast medium from the vascular to extravascular space [12-14].

Comparing the application of the Patlak model to PCT and MRI techniques, the main advantage of PCT over MRI is that it is quantitative. Indeed, because DSC T2* MRI relies on susceptibility, the relationship between the gadolinium concentration and the measured signal is not linear, but logarithmic. In pixels such as the one at the center of the superior sagittal sinus, the concentration of gadolinium achieved is such as the signal not only drops, but crashes, and the tip of the time-signal curve is lost. As a result, no accurate reference pixel can be found to apply the model initially described by Ladurner and Zilkha to calculate quantitative CBV values [18, 19]. As a consequence, only relative CBV measurements are afforded by DSC T2* MRI, whereas quantitative results can be achieved with PCT. The same observation is true for the MTT, and for the CBF, calculated as the CBV/MTT ratio. Again, because DSC T2* MRI relies on the susceptibility
induced by a gradient of magnetic fields between two compartments, signal-intensity curves cannot be recorded within one single compartment, but only at the border between two compartments. Typically, signal-intensity curves cannot be recorded at the center of an arterial lumen, but only in the immediate vicinity of an artery, where signal is also contributed to by the brain parenchyma. As a result, no reliable arterial input function can be selected with DSC T2* MRI (as opposed to PCT). This compromises the reference arterial input function essential to the deconvolution operation leading to quantitative measurements of perfusion and Patlak permeability [20]. As a result, in the clinical settings, PCT-derived permeability measurements are quantitative, automatic and computerized, whereas DSC T2* MRI-based description of blood-brain barrier permeability is at best qualitative, and relies on a visual interpretation of the time-intensity curves. An alternative method to achieve quantitative measurements of blood-brain barrier permeability using MRI is based on a dynamic T1-weighted approach [11], but this technique does not yield accurate measurements in the setting of neoplasms with high vascularity and high permeability, such as extra-axial tumors. At the present time, one advantage of MRI is to afford a better, whole-brain spatial coverage. On the contrary, PCT spatial coverage is limited, but this may change in the near future as a result of the advent of multi-detector, wide-coverage CT scanners. Finally, another advantage of PCT over MRI is that PCT measurements are not affected by hemorrhage, calcification or post-surgical metallic implants, because the attenuation related to blood or calcium (including the beam hardening) is constant during the data acquisition, and the first step in the perfusion-CT data post-processing consists in the subtraction of the baseline, constant attenuation in each pixel. Moreover, this constant attenuation does not interfere with the increase in density related to the transit of iodinated contrast material. On the other hand, as mentioned above, DSC MRI relies on susceptibility, and blood products or calcifications are going to generate blooming that does interfere with the decrease in signal related to the transit of gadolinium. In conclusion, these two case reports illustrate the potential of PCT-based measurement of the blood-brain barrier permeability to characterize the brain tumors vessels. These measurements have of course to be validated in large prospective studies, as well as their relevance in the selection patients for and the monitoring the effects of anti-angiogenic therapies.

REFERENCES