Perfusion computed tomography of intracranial meningiomas: In vivo correlation of cerebral blood volume and vascular permeability

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Abstract

Background
A noninvasive method to predict the grade of a meningioma would be desirable since it would anticipate information about tumour nature, recurrence and improve tumour management and outcomes. The aim of the present study was to assess the ability of perfusion computed tomography (PCT) technique in predicting the meningioma grade before surgery. Data from PCT, such as cerebral blood volume (CBV) and permeability surface (PS), were correlated with immunohistolopathological information.

Methods
Twenty-three patients with a diagnosis of intracranial meningioma underwent PCT for pre-surgical evaluation of CBV and PS. During surgery, samples from the centre and periphery of the tumour were obtained. Two correspondent regions of interest (ROIs) were drawn on CBV and PS maps. Central and peripheral CBV and PS mean values were calculated. PCT parameters were correlated to CD-34 and endoglin.

Results
There was a positive correlation between PS and CD-34. No correlation was found between PS values and endoglin, CBV values and CD-34 and endoglin values.

Conclusion
Our findings suggest that PCT may support conventional morphological imaging in predicting meningioma grading before surgery.

Keywords: Meningioma, perfusion computed tomography, neoangiogenesis, CD-34, endoglin, permeability surface-area product
**Introduction**

Meningioma is one of the most common kinds of intracranial tumour, representing 34% of all the intracranial neoplasms.  

Most of meningiomas are benign and originate from non-neuroepithelial progenitor cells, the arachnoidal cap cells. As a subgroup of arachnoidal cells, the arachnoidal cap cells form the outer layer of the arachnoid mater and the arachnoid villi. They are also involved in the resorption of cerebrospinal fluid into the dural sinuses and veins.

According to the World Health Organization (WHO) 2007 classification system, meningiomas are classified into three grades: Grade I meningiomas are benign and slow growing tumours; Grade II (atypical) and Grade III (anaplastic) meningiomas are histologically aggressive. The grading has implications on management and prognosis because of atypical and anaplastic meningiomas often recur and have a poorer prognosis compared with grade I tumours.

There is no specific neuroradiological pattern on traditional computed tomography (CT) scan neither on magnetic resonance imaging (MRI) that allows meningioma grading to be established, unless necrosis or haemorrhage areas are detected. Advanced imaging techniques such as perfusion MRI or perfusion computed tomography (PCT) can provide useful information about meningiomas grading, because of perfusion parameters indirectly reflect the microvessel density (MVD) of the tumours.

Perfusion studies are obtained by monitoring the first passage of an iodinated contrast agent bolus through the brain vessels. The distribution of the contrast medium following injection is determined by the microvascularization and the diffusion across the endothelial membrane.

Regional cerebral blood volume (rCBV) reflects an assessment of tumour vasculature and perfusion and it can be considered as a good surrogate marker for MVD, revealing information about the total amount of vessels in the tumour including neo vessels and the native vasculature. Permeability surface-area (PS) product indicates the diffusion of contrast agent moving from the blood vessels into the interstitial space caused by tumour-induced blood-brain barrier (BBB) disruption. Therefore, PS value is a valid in vivo measurement of the abnormal tumour-vessels permeability with the strongest correlation with the tumour grade.

The aim of the present study was to assess the use of PCT technique in predicting the meningioma grade before surgery, by evaluating the correlation between CBV and PS with CD-34 and endoglin, immunoistochemical markers of neoangiogenesis in meningiomas.

**Materials and methods**

**Study population**

From January 2013–November 2013 we prospectively evaluated 23 patients with a neuroradiological diagnosis of intracranial meningioma. The entire study has been approved by the University Ethics Committee before patient recruitment; written informed consent of all patients was obtained.

They were 7 males and 16 females, from 40–81 years old with a mean age of 60.2 (±11.1) years. Most of the tumours were supratentorial. Some of the lesions showed few or scattered calcifications. All patients underwent PCT for pre-surgical evaluation of tumour blood volume and PS product. Patients underwent surgical treatment and specimens from the centre and the periphery of the tumour were collected for histopathological analysis.

**Table 1.**
Evaluation of meningioma characteristic in each patient.

**PCT technique and image processing**

CT examination was performed by 64 multi-row CT scanner (Somatom Definition 64 Siemens, Erlangen, Germany). A baseline non-contrast CT head study was done to localize the tumour, before obtaining a perfusion scan. For the perfusion scan, 50 ml volume of a non-ionic contrast agent (Visipaque-320) was injected at a rate of 5 ml/s by using an automatic power injector through an 18-gauge intravenous line of an antecubital vein. Five seconds following the injection, a continuous scanning was initiated and, from the selected axial section, 80 consecutive images were acquired with a time interval of 1 s. PCT parameters were: 80 kV, 180 mA, 512 × 512 matrix, field of view 20–25 cm, 4 × 5 mm sections with 10 mm-thick sections reformatting. The duration of the total data acquisition was of 80 s.

All patients tolerated PCT well and showed no adverse reaction to the rapid bolus injection of contrast.

Perfusion CBV (ml/100 g) and PS (ml/100 g/ min) maps and maximum intensity projection (MIP) images were generated in a workstation, based on unidirectional two-compartment Patlak method, by using a post-processing commercial software package (Volume Perfusion CT, Siemens, Erlangen, Germany). We also calculated cerebral blood flow (CBF), time to start (TTS), time to peak (TPP), mean transit time (MTT) and time to drain (TTD). In all patients we used the superior sagittal sinus as the venous output function and the artery with the greatest peak and slope on time-attenuation curves as the arterial input function. The shape of the arterial input function was automatically generated from branches of middle cerebral artery (MCA) and anterior cerebral artery (ACA), the peak of the input function was normalized to the peak of the superior sagittal sinus.

**Image analysis**

Two regions of interest (ROIs) were drawn on the colorimetric perfusion maps for each patient. ROIs were initially placed on the MIP images: the first ROI delimiting the central portion of the tumour, the second, a free-hand ROI, delimiting the periphery of the neoplastic lesion (Figure 1). The ROIs were then automatically copied onto the perfusion maps. Corresponding CBV and PS middle and standard deviation values of the central and the peripheral portions of the meningioma were calculated.

![Figure 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757289/) Regions of interest (ROIs) positioning in a 67-year-old female with a right parafalcine meningioma.

**Histopathological examination**

At surgery, a peripheral and a central specimen were taken from 15 tumours. Only one specimen for each tumour was obtained in eight cases. Samples were formalin fixed and paraffin embedded for the histological examination and immunohistochemistry. In detail, from each paraffin block, serial 4 µm tissue sections were cut and stained with conventional haematoxylin and eosin stain or processed for immunohistochemical procedures involving the endothelial marker CD-34 and the specific marker for neoangiogenesis endoglin. Sections were successively incubated with the primary monoclonal antibodies against endoglin (DAKO Corporation, Denmark, clone SN6h, w.d. 1:50) and CD-34 (DAKO Corporation, Denmark, clone QBEnd10, w.d. 1:50). The bound primary antibodies were visualized by LSAB kit (Dako Cytomation, Glostrup, Denmark) according to the manufacturer’s instructions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757289/
As previously described, the quantification of microvessel was performed. Briefly, the three most vascularized areas detected by endoglin or CD-34 were initially selected (so-called hot spots) under 40× field. Microvessels were counted in each of these areas under a 400× field. Single endothelial cells or cluster of endothelial cells, with or without a lumen, were considered to be individual vessels. The mean value of three 400× field (0.30 mm²) counts was recorded as the MVD of the section. The MVD value was converted into the mean number of microvessels/mm² for the statistical analysis.

Using a Zeiss microscope the vessels were counted by two observers, independent and blinded for the CT perfusion data.

Statistical analysis

Statistical analysis was performed using SPSS statistical software package (version 19; SPSS, Inc., Chicago, Illinois, USA). To test whether CBV and PS were able to predict meningioma grade, we correlated values sampled both in central as well as in peripheral regions to CD-34 and endoglin histochemical markers obtained from the same regions. To this end, we evaluated and tested, for each pair, Pearson’s coefficient (PCC); this analysis was possible because all variables were normally distributed according to Shapiro-Wilk test (results not shown). Values of \( p \) smaller than 0.05 were considered statistically significant; multiple comparison issue was accounted for by means of Bonferroni correction.

Results

Data from 21 out of 23 patients were eligible for statistical analysis; one case (patient no. 18) was excluded because that subject presented a calcified meningioma for which we could not measure CBV and PS; another one (patient no. 5) was excluded because the subject has an angioblastic meningioma (CBV values obtained were significantly higher compared with those presented in other patients).

CBV and PS mean and standard deviation values were calculated drawing ROIs in the solid part in patient no. 19, who showed a meningioma with some cystic central components. Eventually, in two patients (patient nos 2 and 4), who had partially calcified meningiomas, we obtained only a single ROI.

In eight patients it was not possible to evaluate peripheral values for CD-34 and endoglin. Hence, a total of 21 samples were used in analyses related to central regions, whereas for peripheral areas we used 13 left samples. In our study there was a positive correlation between PS and CD-34 central values (\( PCC = 0.577, p = 0.0062 \) uncorrected, \( n = 21, R^2 = .333 \)) (Figure 2); on the other hand, no statistically significant correlation was found between PS and CD-34 peripheral samplings (\( PCC = 0.287, p = 0.341 \) uncorrected, \( n = 13 \)). Moreover, no correlation was found between PS values and endoglin values, neither in central samples (\( PCC = 0.380, p = 0.090 \) uncorrected, \( n = 21 \)) nor in peripheral samples (\( PCC = 0.572, p = 0.041 \) uncorrected, \( n = 13 \)). No significant correlations were found between CBV values and CD-34 and endoglin values, neither considering central samples (\( PCC = 0.365, p = 0.103 \) uncorrected, \( n = 21 \) and \( PCC = 0.254, p = 0.267 \) uncorrected, \( n = 21 \) respectively), nor considering peripheral samples (\( PCC = 0.416, p = 0.157 \) uncorrected, \( n = 13 \) and \( PCC = 0.621, p = 0.023 \) uncorrected, \( n = 13 \) respectively).

Discussion

![Figure 2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757289/)

Scatterplot of CD-34 and permeability surface-area (PS) product values sampled from regions of interest (ROIs) segmenting central parts of 21 meningiomas; regression line is displayed as well (\( R^2 = 0.333 \)).
Our study showed a significant statistically correlation between PS, a PCT parameter, and CD-34, an immunohistochemical marker of neoangiogenesis in meningioma.

Compared with a MR perfusion study, PCT is a fast and low cost examination. The technique provides high spatial resolution and it represents a valid alternative for the assessment of cerebral haemodynamics.\textsuperscript{11,12,13,29}

PCT is performed by monitoring the first passage of an iodinated contrast agent bolus through the brain vessels. Conceptually, the contrast-medium pharmacokinetic involves three brain compartments: intracellular, intravascular and interstitial. The iodinate molecules of the contrast-medium do not cross the cellular membrane and do not reflow from the extravascular into the intravascular space. Therefore, for the evaluation of the enhancement, the intracellular space can be ignored and just the unidirectional tracer distribution, into the two remaining compartments (intravascular to interstitial), should be considered.

PCT provides a linear relation between density changes and tissue concentration of the contrast agent such as to make reliable the quantification of PCT parameters. CBV is defined as the total volume of blood in a given region of the brain and it is calculated as units of ml of blood per 100 g of brain tissue (ml/100 g). The CBV maps are obtained from the mathematic integration of the area under the concentration versus time curve. CBV is a good surrogate marker for MVD, revealing information about the amount of total vessels (neovessels and native vasculature), but not of active endothelial cells proliferation.\textsuperscript{13}

PS characterizes the diffusion of the contrast agent from the neoangiogenic blood vessels into the interstitial space due to tumour-induced BBB disruption and, therefore, it has a strongest correlation with the tumour grade.\textsuperscript{13,29}

In the literature, previous data show the usefulness of PCT for the assessment of intra-axial tumour vascularity. Malignant tumours are associated with increased angiogenic activity and neovascularization, resulting in increased blood volume and hyperpermeability related to the presence of immature vessels. Increased vascular permeability is also correlated with malignancy. It evolves as a surrogate marker of tumour angiogenesis and tumour.\textsuperscript{11,14,22,30} Higher permeability is associated with higher tumour grade and it can be considered as an histologically pattern of blood-brain barrier disturbance.\textsuperscript{14,22}

Several lines of evidence support a good correlation between PCT parameters and histological markers of angiogenesis, such as MVD, in gliomas with a resulting role of PCT in the assessment of neoplastic grading.\textsuperscript{11,13,14,20,22,31,32} For extra-axial tumours it has been demonstrated the correlation between PCT parameters (i.e. CBV and PS) and MVD thus suggesting a possible role of PCT imaging in anticipating the diagnosis between benign meningiomas and haemangiopericytomas.\textsuperscript{21}

In our study we observed some different PCT patterns of CBV and PS parameters with a different vessel distribution between the centre and the periphery of the lesion (\textit{Figures 3} and \textit{4}). Probably these perfusion patterns were related to the different number, and not to the homogeneous distribution, of tumoral vessels in the centre and in the periphery of the meningioma. The neoangiogenic vessels are also characterized by different permeability levels. In our experience we found a strong association between PS values and immunohistochemical endothelial markers. PS values showed a significant statistically positive correlation with CD-34 expression and tumour aggressiveness and grade.

\textbf{Figure 3.}
Different cerebral blood volume (CBV) patterns in three different cases of meningioma: (a) CBV values are similar in the whole right pterion meningioma of a 55-year-old female; (b) higher CBV values are visible in the central part of a tuberculum sellae ...

\textit{https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757289/}
Figure 4.
Meningioma permeability surface-area (PS) product patterns in three different cases: (a) PS values are similar in the whole left frontal convexity meningioma of a 52-year-old female; (b) higher PS values are visible in the central part of a ethmoidal ...

The positive correlation between the PCT parameters and the immunohistochemical markers of neoangiogenesis, supports the usefulness of PCT values for the pre-surgical evaluation of the meningioma grading. In a presumed high-grade meningioma, a more extensive resection is warranted; furthermore, the use of fractionated radiotherapy or stereotactic single-dose radiosurgery could be necessary for meningiomas that are incompletely resected, recurrent, or atypical or anaplastic.\textsuperscript{6,33} PCT data moreover could be useful to manage patients with small size, incidentally-found meningiomas, to better assess the biological behaviour of the tumour and to postpone the neurosurgical treatment in selected cases.\textsuperscript{34}

PCT presents advantages compared with MR perfusion technique the most important being its linear signal intensity change in response to the tissue concentration of the contrast agent.\textsuperscript{35} Furthermore, it offers multiple perfusion parameters that can be obtained with a single acquisition.\textsuperscript{35}

Limitations of PCT are the radiation dose to the patient and difficulties during the osseous segmentation in diffusely calcified meningioma, in which CBV and PS are not calculable, and in skull base meningioma.

**Conclusion**

PCT can provide good information on meningiomas neoangiogenesis before surgery. This technique could be complementary to the conventional magnetic resonance imaging for the differentiation between atypical/malignant meningiomas from lower grade lesions, allowing a better management of surgery and post-operative therapies.

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**Conflict of interest**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical standards**

The authors declare that this study complies with the current laws of the country in which it has been performed (Italy).

**References**


