Utility of the kurtosis for the assessment of brain tumors

Poster No.: C-0734
Congress: ECR 2011
Type: Scientific Exhibit
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Keywords: Head and neck, Neuroradiology brain, Computer applications, MR, MR-Diffusion/Perfusion, Computer Applications-Detection, diagnosis, Contrast agent-intravenous, Statistics, Neoplasia, Tissue characterisation
DOI: 10.1594/ecr2011/C-0734

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Purpose

Astrocytomas are histopathologically heterogeneous tumors, in which low and high grade areas coexist in the same tumor, being the latter those that define the true grade of the tumor. Vascular proliferation is a histological descriptor that is used to classify them [1]. These newly formed vessels have abnormalities in their development, maturation and distribution within the tumor tissue. Perfusion studies with MRI are able to provide information on the alteration of angiogenesis and tumor vessel permeability. In fact, parameters derived from quantitative analysis of perfusion MRI contribute to classify the tumors more accurately than conventional MRI, in which only morphological criteria are applied [2,3].

Several studies have shown a good correlation between the cerebral blood volume (CBV) and the tumor grade of astrocytomas, mainly to separate low-grade astrocytomas (II) from high grade (III and IV) [2,4-6]. The relationship between the tumor grade and the capillary permeability ($K_{trans}$) is more controversial, with controversial results [7,8]. Histological complexity of the lesion also results in an uneven distribution of perfusion parameters, a fact that can be seen in the obtained parametric maps. The extent of this heterogeneity may be useful to grade gliomas or to improve clinical management [9,10].

Homogeneous distributions of histograms show a prominent peak around the average value. However, for the heterogeneous distributions, histograms show a more irregular, shape because the frequencies are much more dispersed. The kurtosis is a statistical descriptor of the histogram shape which provides an idea of how peaky the distribution is. High values of kurtosis indicate distributions with a high peak, i.e. with very concentrated values around the average. By contrast, low values of kurtosis are related to increased dispersion, i.e., greater heterogeneity of values.

The aim of this study is to evaluate the utility of the kurtosis analysis of quantitative MR perfusion parameters as a heterogeneity biomarker for the classification of brain tumors according to their aggressiveness.
Methods and Materials

Subjects

This retrospective study was performed from MR perfusion studies of 45 patients (34 men and 11 women) with astrocytomas diagnosed histopathologically. The diagnosis, based on the classification of brain tumors proposed by the World Health Organization, was obtained after surgical resection in 26 (57.7%) and neuronavigation-guided biopsy in 19 patients (42.3%). The distribution by grade was 8 patients with grade II, 8 were grade III and 29 grade IV. We excluded grade I or pilocytic astrocytomas. Patients were between 26 and 74 years old (56.9 ± 12.3 years, mean ± standard deviation). No patients had received cancer treatment prior to image acquisition and imaging studies were performed before the surgical approach.

No specific consent was sought from the hospital Ethics Committee to carry out the work, since the MRI studies of the patients were within normal clinical practice. Any personal information concerning patients was removed for the analysis of the images.

Image acquisition

MRI studies were performed using a 1.5 T (Philips Intera, Philips Healthcare, The Netherlands) with an 8-channel head coil. All patients underwent a conventional study, with a T2* dynamic-susceptibility sequence after the administration of a contrast agent. We used a gradient echo EPI sequence (TR 836 ms, TE 30 ms, flip angle 40°, slice thickness 7 mm and a 128x128 matrix (in plane resolution of 1.8 x1.8 mm), craniocaudal coverage of 13-14cm (19-20 slices), 40 volumes @2.4 s/volume). Gadodiamide (Omniscan, GE Healthcare, USA) was used as contrast agent at a dose of 0.2 mmol/kg @5 ml/s, with 30 ml of physiological saline flush at the same rate. Contrast administration was performed at the start of the acquisition of the third sequence of volumes. The acquired images were anonymized and transferred to a workstation for post-processing [11].

Image analysis

Regions of interest (ROIs) were manually placed at the tumor, the peritumoral and the contrallateral areas. The middle cerebral artery was selected as input function. The uptake curves were extracted and analyzed pixel-by-pixel to obtain the cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), transfer constant (K_{trans}), washout constant (k_{ep}), interstitial volume (v_e) and vascular volume (v_p) [12-14].

Statistical analysis
We performed two ANOVA tests to study differences between groups. In the first test we compared the three ROIs for each tumor grade. In the second test we compared the three tumor grades for each of the ROI.

In each test the mean and kurtosis of the distributions were analyzed separately. A p-value < 0.05 was considered as statistically significant.
Images for this section:

**Fig. 0:** Figure 1. Selection of the regions of interest: middle cerebral artery as arterial input function (red), tumor (blue), peritumoral area (green) and healthy contralateral area (yellow).

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Results

In the comparison of regions of interest for each tumor grade statistically significant differences were obtained between tumor, peritumoral and healthy regions for $K^{\text{trans}}$ ($p < 0.001$), $v_e$ ($p = 0.045$), CBV ($p < 0.001$), CBF ($p < 0.001$) and for the kurtosis of $k$$_{ep}$ ($p = 0.046$) and MTT ($p = 0.035$), in the case of grade III tumors; and for $K^{\text{trans}}$ ($p < 0.001$), $v_p$ ($p = 0.001$), CBV ($p < 0.001$), CBF ($p < 0.001$) and kurtosis of $K^{\text{trans}}$ ($p = 0.023$), $k$$_{ep}$ ($p = 0.001$), $v_e$ ($p = 0.038$), MTT ($p = 0.006$) and CBF ($p = 0.014$), in the case of grade IV tumors. The other parameters did not provide significant differences.

In the comparison of different tumor grades for each region of interest there were statistically significant differences between grades II, III and IV for $K^{\text{trans}}$ ($p = 0.006$), $k$$_{ep}$ ($p = 0.021$), $v_e$ ($p = 0.003$), CBV ($p < 0.001$) and CBF ($p < 0.001$) for the tumor region. For the other parameters, including the values of kurtosis, no statistically significant differences among the three tumor grades were found for any of the regions.
Images for this section:

![Images showing delayed contrast-enhanced image of a grade-IV astrocytoma and coloured parametric maps for mean transit time (MTT), cerebral blood volume (CBV), cerebral blood flow (CBF), capillary permeability (Ktrans), washout rate (kep), interstitial space fraction (ve) and vascular space fraction (vp).](image)

**Fig. 0:** Figure 2. Delayed contrast-enhanced image of a grade-IV astrocytoma and coloured parametric maps for mean transit time (MTT), cerebral blood volume (CBV), cerebral blood flow (CBF), capillary permeability (Ktrans), washout rate (kep), interstitial space fraction (ve) and vascular space fraction (vp).

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Fig. 0: Figure 3. Ktrans normalized histograms for the tumor, peritumoral and healthy areas of a grade-IV tumor. It can be seen that the tumor and the peritumoral histograms are less peaky (i.e. they have lower kurtosis) than the healthy area histogram.

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Conclusion

The kurtosis of quantitative perfusion-derived parameters cannot be used to classify tumors according to the aggressiveness. However, it can be used to assess the regional heterogeneity of grade-IV and grade-III tumors.
References


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