Differentiating High-Grade and Low-Grade Neuroepithelial Brain Tumors: Stereotactic Biopsy versus Proton MR Spectroscopy

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Synopsis: At present, grading of unresectable brain tumors is performed on biopsy samples obtained by CT- or MR-guided stereotactic biopsy. The present prospective study tested the hypothesis that single voxel ^{1}H MRS and stereotactic biopsy are of equivalent diagnostic value, with regard to differentiating high-grade from low-grade brain tumors. In a series of 80 consecutive patients observer-independent classification of tumor ^{1}H MR spectra and histopathology performed on stereotactic biopsy samples yielded consistent results in 72 cases (concordance: $p<0.0005$; Cohens Kappa: 0.76; sensitivity and specificity: 89% and 94%). The result indicates that both methods are of similar value with respect to differentiating high-grade and low-grade brain tumors

Introduction:

Therapy and prognosis differ considerably between high-grade and low-grade neuroepithelial brain tumors. Hence, histopathological confirmation of tumor grade is essentially required, even if tumors are located in inaccessible or functionally important areas. At present, grading of unresectable tumors is performed on biopsy samples obtained by CT- or MR-guided stereotactic biopsy. Besides potential surgery-associated complications (1), biopsy samples are frequently subjected to sampling errors resulting in an inadequate grading of unresectable tumors in up to 5% to 15% (2). The goal of the present prospective study was testing the hypothesis that ^{1}H MRS and stereotactic biopsy are of equivalent diagnostic value, with regard to differentiating high grade from low-grade neuroepithelial brain tumors.

Methods:

Study design: The whole study was subdivided into two phases. During the initial approximately twelve-month phase a database consisting of 40 ^{1}H MR spectra obtained from completely resected neuroepithelial brain tumors was established. These baseline data were used to determine classification rules, which are useful to differentiate between high-grade and low-grade neuroepithelial brain tumors. In the subsequent approximately 36-month phase 83 consecutive patients with imaging and history suggestive for neuroepithelial brain tumors underwent a spectroscopic examination of the lesion prior to stereotactic serial biopsy. These consecutive cases were observer-indepently classified as either "high-grade" or "low-grade" according to the preestablished classification rules. All histological diagnoses in the study were performed in accordance with the WHO classification and validated by considering an at least 12-month post surgical follow up (range: 12 to 54 month).

^{1}HMRS: ^{1}HMRS and imaging studies were performed at the Institute of Neuroradiology, University of Frankfurt, 1 to 5 days prior to stereotactic surgery using a clinical whole body 1.5 Tesla MR-Scanner. In detail the imaging and spectroscopy protocol used has been described elsewhere (3). Briefly, single voxel ^{1}H MRS (PRESS, TE 135ms, TR 1500ms, 128 to 258 acquisitions) was performed immediately after a standard MR imaging (MRI) exam. Based on MRI-criteria the volumes of interest (VOI, size 2.1 to 8.6 cc) were placed within viable tumor avoiding substantial partial volume effects with necrotic or cystic areas and/or tumor-adjacent brain tissue. Spectral data were analysed in the time domain using the MRUI software applying constraints based on prior knowledge files of the major resonances of choline (Cho), creatine/phosphocreatine (tCr), N-acetyl-L-aspartate (NAA), lactate (Lac) and lipid (Lip). Absolute metabolite concentrations (institutional arbitrary units) were calculated from the measured signal intensities applying correction factors for voxel size, number of acquisitions, and coil loading.

Spectral database: The spectral baseline data were acquired in order to establish classification rules that allow an objective, observer-independent differentiation between high-grade and low-grade neuroepithelial brain tumors. The classification rules (i.e., linear discriminant functions) were established by linear discriminant analysis (LDA). Eligibility requirements for spectra for being included in the baseline data were as follows: i) sufficient spectral quality, i.e., local shim of less than 10 Hz full width at half maximum plus a variation coefficient of the time domain fit of less than 10% for the Cho-resonance, which is usually the most prominent resonance of tumor spectra; ii) spectra must be obtained from completely resected neuroepithelial brain tumors in order to ensure that histological confirmation of tumor type and grade is performed on a sufficient amount of representative tumor tissue; iii) Consistence of histopathological grade and clinical progress of the disease.

Prospective evaluation of the concordance between ^{1}H MRS and stereotactic biopsy: For purpose of prospective evaluation of the concordance between ^{1}H MRS and stereotactic biopsy a consistent study protocol applying the same criteria of spectral quality as described for the baseline data was used. Eligibility requirements for patients for the enrolment into the second phase of the trial were as follows: i) history and MRI suggestive for neuroepithelial brain tumors; ii) no primary indication of complete tumor resection either due to the location of the lesion or the extent of tumor growth; iii) requirement for histological verification of histotype and grade performed on biopsy samples obtained by stereotactic surgery. A total of 80 out of 83 consecutive patients met the eligibility requirements and fulfilled the above standards of spectral quality, while three were rejected due to poor quality of the ^{1}H MRS examen. The linear discriminant functions derived from the baseline data were used to observer-independently classify tumors either low-grade (i.e., grade I or II WHO) or high-grade (i.e., grade III or IV WHO) in order to avoid observer bias within the frame of the evaluation of ^{1}H MRS.

Statistics: LDA was performed to establish the classification rules and to objectively discriminate low grade and high grade tumors (s. above). Cohens Kappa statistics was used to test the hypothesis of a high concordance of both methods (i.e., ^{1}H MRS and histopathological grading made on stereotactic biopsy samples). Using the histopathological diagnoses plus clinical data as "Goldstandard" the sensitivity and specificity of ^{1}H MRS in differentiating low grade and high grade tumors.

Results and Discussion:

Stereotactic serial biopsy was successfully performed in all cases assessing a mean number of 14 samples (range 7 to 24). Over all, histopathological grading on stereotactic biopsy samples revealed 21 low-grade tumors (i.e., WHO grade I or II) and 59 high-grade tumors (i.e., WHO III or IV). Grading on spectroscopic data revealed 25 low-grade tumors and 55 high-grade tumors. In 8 out of 80 cases (1 low-grade tumor, 7 high-grade tumors) spectroscopic grading did not match with histopathological grading, while 72 cases revealed a consistent result for both methods resulting in a highly significant concordance ($p<0.0005$; Cohens Kappa: 0.76).

All diagnoses "high-grade tumor" made on stereotactic biopsy samples were confirmed by the clinical progress of the disease. In contrast, 5 patients histopathologically diagnosed as suffering from low-grade tumors progressively worsened, which is by definition not consistent with the biological behaviour of a low-grade tumor. In order to assess the true diagnostic value of ^{1}HMRS these cases were rated as inappropriate histopathological grading potentially caused by sampling errors. Using clinical data plus histopathological diagnoses as "gold standard" the resulting sensitivity and specificity of ^{1}H MRS to differentiate high-grade from low-grade tumors yielded 89% (95% confidence interval (CI): 83%-95%) and 94% (CI: 85%-100%) respectively. The significant concordance between single voxel ^{1}H MRS and stereotactic biopsy found in the present study, suggests ^{1}H MRS as a valid method to guide the management of patients if complete tumor-resection is not feasible or is not the appropriate initial treatment. Since ^{1}H MRS provides a completely non-invasive procedure it may serve as the method of choice in cases where even stereotactic biopsy is not feasible or associated with enhanced surgical risk.

References:

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