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Serial Stereotactic Biopsy of Brainstem Lesions in Adults Improves Diagnostic Accuracy Compared to MRI Only

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key words: brainstem glioma, stereotaxy, biopsy, MRI

Abstract:

Objective: The aim of the current prospective study was to analyse the validity of MRI based diagnosis of brainstem gliomas which was verified by stereotactic biopsy and follow-up evaluation as well as to assess prognostic factors and risk profile.

Methods: Between 1998 and 2007 all consecutive adult patients with radiologically suspected brainstem glioma were included. The MRI-based diagnosis of the lesions was made independently by an experienced neuroradiologist. Histopathological evaluation was performed in all patients from paraffin embedded specimen obtained by multi-modal image guided stereotactic serial biopsy technique. Histopathological results were compared with prior radiological assessment. Length of survival was estimated with the Kaplan Meier method and prognostic factors were calculated using the Cox model.

Results: Forty-six adult patients were included. Histological evaluation revealed pilocytic astrocytoma (n=2), WHO Grade II glioma (n=14), malignant glioma (n=12), metastasis (n=7), lymphoma (n=5), cavernoma (n=1), inflammatory disease (n=2) or no tumor/gliosis (n=3). Perioperative morbidity was 2.5% (n=1). There was no permanent morbidity and no mortality. All patients with “no tumour” or “inflammatory disease” survived. Patients with low-grade glioma and malignant glioma showed a 1-year survival rate of 75% and 25%, respectively; 1-year survival rate for patients with lymphoma or metastasis was 30%. In the subgroup of a verified brainstem glioma, negative predictors for length of survival were: higher tumour grade (p=0.002) and Karnofsky performance score (KPS) ≤ 70 (p=0.004).

Conclusion. Intra-axial brainstem lesions with radiological pattern of glioma represent a very heterogeneous tumour group with completely different outcome. Radiological features alone are not reliable for diagnostic classification. Stereotactic biopsy is a safe method to obtain a valid tissue diagnosis, which is indispensable for treatment decision.

Key words: brainstem, glioma, magnetic resonance tomography, stereotactic biopsy

Introduction

Intra-axial brainstem gliomas in adults represent about 2% of all brain tumours¹. In children the proportion of these tumour is as high as 20-25%^{1,2}. Several reports deal with brainstem gliomas in children regarding their biological behaviour, MRI findings, prognostic factors and management³⁻⁹.

On the contrary, features and biology of brainstem gliomas in adults are less well known. Only few reports focus on this tumour entity with only one recent publication¹⁰. In most of these studies treatment decisions are based on MRI features only and do not include a histopathological diagnosis. Most authors regard a biopsy of intrinsic brainstem tumours as being too dangerous¹¹⁻¹³ and consider imaging methods as sufficiently reliable¹⁴. Thus the impact of MRI findings on treatment decision for brainstem tumours is very high, but the accuracy of MRI based diagnosis of brainstem gliomas has not been verified sufficiently by histopathological findings up to date.

In current literature brainstem gliomas are differentiated by MRI characteristics into two sub-groups: a) focal tumours, which are typically well marginated on MRI, occupy less than 50% of the axial diameter of the brainstem and frequently show contrast enhancement. These tumours are usually regarded as low grade tumours and addressed a good prognosis. b) diffuse brainstem tumours, which are poorly marginated, rarely enhance with contrast and occupy more than 50% of the axial diameter of the brainstem. While the first group is normally interpreted as pilocytic glioma with rather benign biology, the latter are mostly considered as malignant glioma¹⁴.

The aim of this prospective study was to analyse and validate the accuracy of conventional MRI based classifications of brainstem gliomas. This was achieved by comparing radiological diagnosis with histopathological findings. In this context we also assessed risk profile as well

as diagnostic and prognostic relevance of a tissue diagnosis obtained by stereotactic biopsy in patients with brainstem lesions. For evaluation of prognostic factors length of survival was correlated with the obtained tissue diagnosis and all relevant pre-treatment clinical and neuroradiological parameters.

Clinical Material and Methods

Patients

Between April 1998 and September 2007 all consecutive adult patients were included in this study if the epicentre of a suspected glioma was located in the brainstem. Patients with radiological and clinical evidence for disease other than glioma were excluded. MRI was evaluated with a lesion being suspicious for brainstem glioma (high or low grade) in all patients enrolled.

MRI based assessment and diagnosis was performed independently by an experienced neuroradiologist (M.H.) twice, with and without knowledge of clinical data (except for histology). According to current radiological guidelines, brainstem glioma was defined by the location of the lesion (i.e. mesecephalon, pons, medulla oblongata) on imaging data (axial and sagittal T2 and T1 weighted images (with and without gadolinium)), performed with a 1.5 Tesla scanner (Magnetom VISION, Siemens, Erlangen, Germany). Tumours were assessed according to current guidelines¹⁵ and distinguished as being focal (suspected low grade) or diffuse (suspected high grade). They were judged focal when being well marginated, showing contrast enhancement and occupying less than 50% of the axial brainstem diameter. Poorly marginated tumours, with an extension of more than 50 % of brainstem diameter, were classified as diffuse. The lesion was considered extended if it involved more than one segment of the brainstem (e.g. medulla oblongata, pons).

For histological proof of diagnosis of brainstem glioma all patients underwent stereotactic biopsy. MRI/CT-guided stereotactic biopsy was performed as described previously¹⁶. A modified Riechert Stereotaxy System (MHT, Freiburg, Germany) was used. Target definition for the biopsy procedure was based on MRI. CT and MRI images were fused on a Brain Lab work station. (Brain Lab image fusion software, Brain Lab, Heimstetten, Germany) A six millimeter burr hole was made and serial biopsies along an exactly defined trajectory

representative for the area of interest were taken using micro forceps. The average amount of tissue per biopsy specimen was 1 mm^3 and the number of specimens taken in one millimeter steps ranged from 5 to 15 samples per patient. Smear preparations of the biopsy specimens were intra-operatively examined by an attending neuropathologist in all patients. After the neuropathologist's statement that the amount of specimen was sufficient for assessment, the biopsy procedure was stopped. The final diagnosis was made from paraffin embedded tissue specimens and the smear preparations (J.H.). Additional immunohistochemical examination and an assessment of the proliferation index were used.

For immediate follow up each patient a) received CT scan postoperatively, which was assessed by a neuroradiologist to confirm stereotaxy marker position and exclude haemorrhage and b) was examined clinically by a neurosurgeon for detection of procedure related symptoms. Clinical follow up was held in 3 months intervals with a minimum follow up of 1 year for all patients. If patients did not show up for follow up, necessary information was obtained by phone interviews. **Median follow-up time for survivors was 33 months.**

Treatment was initiated according to current recommendations and standards: radiotherapy for low grade gliomas and lymphomas, radio-chemotherapy for high grade gliomas, radiosurgery for singular metastasis, antibiotic treatment for abscess, immunosuppression for autoimmune inflammatory disease and no treatment (observation) for *no tumor/gliosis*.

Sensitivity and specificity of conventional MRI imaging for diagnosis of brainstem gliomas was estimated by comparison with histological results.

Statistical analysis

Length of survival was estimated with the Kaplan Meier method. The impact of pre-treatment factors upon survival was analyzed by using the Cox model.

Results

Patient population

Between April 1998 and September 2007 forty-six patients were included (25 male, 21 female). All patients were adults (>18 years). Age ranged from 18 to 78 years (median 43 years). Median follow up was 17 months (range from 1 month to 91 months) (Table 1). Clinical signs included ataxia (n=30), cranial nerve deficit (n=27), hemi paresis (n=19).

Surgical procedure and complications

Three patients received a second biopsy (due to non pathological findings after the first procedure), thus 49 procedures were performed. Surgical approach was frontal extra ventricular in 41 cases and suboccipital transpeduncular in 8 cases. There were two procedure related complications (4%): in one patient a transient wound healing disorder occurred which required no further surgical intervention. One patient showed a postoperative aggravation of a preoperatively already existing ataxia. There were no permanent complications. No patient showed haemorrhage on postoperative CT-scan.

Histopathological results

Histological evaluation revealed pilocytic astrocytoma (n=2), WHO grade II glioma (n=14), malignant glioma (n=12), metastasis (n=7), lymphoma (n=5)(e.g. image 1), cavernoma (n=1), inflammatory abscess (n=1) and an inflammatory demyelinating disease (n=1). The diagnosis *no tumor/gliosis* was achieved in 3 patients (Table 2). In this three cases the stereotactic biopsy was repeated and showed an identical result.

Correlation of histological and radiological findings:

Neuroradiological assessment as glioma differed from histopathological diagnosis in 14 out of 46 patients. In the subgroup of patients with low grade gliomas (Glioma grade I-II) the specificity of MRI was 46,6%, sensitivity was 62,5% (Table 3). In the subgroup of patients harbouring glioma grade III or IV the specificity of MRI was 61,7%, sensitivity 58,3% (Table 4).

For tumour grading radiological assessments were correct in 7/20 (35%) for low grade and in 7/26 (27%) for high grade glioma.

Pathologies different from glioma showed a high variety ranging from other neoplastic diseases (lymphoma [n=5], metastasis [n=7]) to benign lesions (cavernoma [n=1], no tumor/gliosis [n=3]) or inflammatory disease (encephalitis disseminata, abscess [n=2]) (Table 2).

Follow-up/length of survival

All patients with *no tumor/gliosis*, inflammatory disease or pilocytic astrocytoma survived the entire period of observation or at least ≥ 1 year. Patients with WHO grade II glioma showed a 1-year survival rate of 93% while this rate was 42% in patients with malignant glioma (Figure 1). Patients with lymphoma or metastasis had a 1 year survival rate of 33%.

Negative predictors for length of survival in patients with verified brainstem gliomas were a higher tumour grade ($p=0,002$) and KPS ($p=0,004$). Age, duration of symptoms, cranial nerves impairment, level of the tumour, multifocal extension, tumour delineation and contrast enhancement had no significant influence on length of survival (Table 5). Multivariate analysis was not performed due to shortage of events.

Discussion

In the present prospective study we analysed the diagnostic value of conventional MRI-based diagnosis for assessment of presumed intra-axial brainstem gliomas in adult population by comparison with histopathological diagnosis. In this context we further analysed the risk profile for stereotactic brainstem biopsies and identified prognostic factors for survival in these patients.

The diagnostic management of patients with brainstem tumours is discussed controversially. Most authors rely on MR imaging for treatment decision as radiological findings are considered to be sufficiently characteristic and specific¹⁴. Thus histological diagnosis is not warranted in most studies as biopsy of brainstem lesions is considered to be a high-risk procedure¹¹⁻¹³.

In this study patients were enrolled, whose MRI images showed suspected brainstem glioma according to established features^{14;15}. Other brain stem lesions, which appeared already radiologically untypical for glioma were not included in this prospective investigation.

Diagnostic accuracy

Biopsy of those lesions addressed as glioma revealed a histopathological diagnosis differing from the radiological assessment in 18 out of 46 cases by means of differentiating glioma vs. non glioma. This included two patients, where the lesion turned out to be of inflammatory nature (with negative CSF parameters). In seven cases metastasis of so far unknown origin was found instead of glioma. In five patients lymphoma was diagnosed as was cavernoma in one patient. Three patients showed no tumour or inflammatory tissue at all but only reactive gliotic tissue possibly linking to previous inflammatory or vascular incidents. Thus, radiological assessment misleadingly classified some potential benign findings as glioma. Considering the completely differing treatment options for low grade glioma (brachytherapy, radiotherapy), high grade glioma (radiotherapy, chemotherapy), abscess (draining, i.v.

antibiotics) and inflammatory lesion (immunosuppression, immunomodulation), the percentage of wrong radiological diagnosis based on established features is extremely high. Thus, wrong decisions for treatment in these patients may result in fatal consequences or at least unnecessary strain.

In the group of radiological high grade gliomas only seven out of 20 patients had a glioma grade III or IV^o while ten patients had low grade (grade I or II) glioma, lymphoma or metastasis. In regard of the therapeutic consequence by means of radiotherapy or radio-chemotherapy also these patients might have gained some benefit from treatment, however, for two patients with no histological evidence for tumour, this treatment based on radiological diagnosis might have been of severe consequence. A similar set was observed in the group of suspected low grade gliomas, where two out of 26 patients showed inflammatory disease. Regarding this high number of incorrect classifications of brainstem lesions by radiological means and the necessity for highly specific therapies for the different pathological entities, MRI alone should not be used for treatment decision making in our opinion.

In this study, all patients were clearly radiologically diagnosed a brain stem glioma. Even then, within this supposedly homogeneous group this diagnosis turned out to be wrong in 60 percent (e.g. image 1). For suspected low grade gliomas MRI specificity was as low as 46,6%, for malignant gliomas it reached 61,7%. **However, it cannot be excluded that the explanatory power of these numbers might have been increased by the involvement of a second independent neuroradiologist.**

Our findings may be interpreted to be in contrast to other studies published. Schumacher et al described 2007 a series of 142 paediatric cases with brain stem lesions reporting a correct classification by the radiologist up to 90%.¹⁷ This may be due to the paediatric patient population in this study, where a different frequency for various tumours is prevalent than in adults. Furthermore, lesions such as metastasis, lymphoma or encephalitis disseminata are

extremely rare in children, thus the histological variety of brainstem lesions is larger in adults with important differences for therapeutic decisions.

For adult patient population there are no recent studies comparing MRI findings with histological diagnosis in brain stem gliomas. The data by Kesari et al.¹⁰ include a high number of patients with brainstem stem tumours but provide histological data only in 53%, a very recent study by Salmaggi et al.¹⁸ included 32 patients with histopathology data in 21. Thus we provide reliable data focussing on the accuracy of conventional MRI in diagnosis of brainstem gliomas for the first time.

New imaging technologies such as MR spectroscopy and positron emission tomography (PET) have been proven to be useful tools for assessing supratentorial gliomas¹⁹⁻²¹ and may improve non invasive diagnosis also brain stem gliomas as well, however, prospective data regarding the accuracy of these methods in this subset of tumours are pending.

It has to be mentioned that radiological assessment even with inclusion of further imaging techniques is subject to an individual range of interpretation, which is not only based on experience but also influenced by the amount of available additional information for the radiologist; a fact which also applies - to lower extent - to pathologists' assessment. Thus, in the light of both, the described variety of pathologies frequently demanding specific treatment strategies and the justifiable procedure-related risk, maximal yield of diagnostic information including stereotactic biopsy should be pursued.

Of further importance is the upcoming role of molecular markers in glioma therapy²²⁻²⁶. As an example, in the treatment of malignant gliomas MGMT promoter methylation has a growing impact on treatment decision, as well as other molecules are assumed to have (e.g. integrins). Although clinical data for the entity of brainstem gliomas and the impact of MGMT on

treatment response are pending, the influence of molecular markers on treatment decision might be significant and will require tissue diagnosis.

Risk profile

Although several authors showed a high variety of histological results in brain stem masses by brainstem biopsy²⁷⁻²⁹, the indication for this procedure is still a matter of debate. Even in the most recent study by Kesari et al. with a high number of patients, histological diagnosis was obtained only in 53%.¹⁰ Many authors claim a very restrictive indication for radiologically unclear lesions due to a presumed high risk profile.

In some published studies a high number of complications by stereotactic brainstem biopsies occurred, reaching up to 10 %¹¹⁻¹³. As a consequence, the authors of these studies propagate a non invasive approach¹²⁻¹⁴. Previous studies from our institution, have proven that stereotactic biopsy is a safe and reliable method with a high diagnostic yield^{30,31}. In this present study there were no major procedure-related complications in spite of the highly eloquent target localisation. Besides one wound healing disorder only one patient showed a slight deterioration of a preoperatively existing ataxia, which recovered slowly during the following months. There were no procedure related bleedings. **The extremely low incidence of complications in the present study may be attributed to a very high number of stereotactic biopsies per year at the authors' institution and a highly standardized work-flow. Thus, our numbers may not reflect the actual risk profile at centers with less experience for stereotactic procedures.**

The diagnostic results obtained by biopsy were conclusive with follow up data. Three patients with no pathological findings in first biopsy underwent re-biopsy with identical histological pattern. The natural course of these patients underlined the absence of a tumour or inflammatory disease and thus confirmed histological diagnosis.

Comparing the reported procedure related risk of a stereotactic biopsy in suspected brainstem glioma with the probability of an incorrect radiological diagnosis and its therapeutic consequences, biopsy not only is justifiable but should be pursued in these patients in our opinion.

Nevertheless, brain stem lesions are comparatively rare findings. Thus it has to be admitted, that a successful and safe biopsy in brainstem regions requires both, a high technical infrastructure, an experienced stereotactic neurosurgeon and a highly standardized workflow for these procedures. Thus biopsies in these eloquent areas should be performed in specialized centres.

Prognostic factors for survival

There are only few current data dealing with the prognosis and prognostic factors in brainstem gliomas in adults.^{10;32} This may be due to the low incidence of these tumours and rarely confirmed histopathological diagnosis. In our series, only tumour grade ($p=0.002$) and KPS ($p=0.004$) reached statistical significance. In the most recent study by Kesari et al¹⁰ a large series of brainstem tumours in adults was evaluated retrospectively in regard of prognostic factors. In Kesari's series also several other parameters e.g. age and duration of symptoms reached significance. Furthermore, survival rate for low grade gliomas in his study was significantly larger than in our series. However, in Kesari's study histological diagnosis was obtained only in 54 out of 101 patients. Considering the limited diagnostic accuracy of MRI for glioma diagnosis, these data may be influenced by a certain number of non glioma lesions which we have shown to have completely different natural course.

Conclusion:

The diagnostic value of conventional MRI imaging in treatment planning of brainstem gliomas in adults is insufficient. Tissue diagnosis is mandatory for adequate treatment decision. Multi-modally guided stereotactic biopsy of brainstem gliomas is a low-risk procedure with a high diagnostic value in experienced hands and thus should be regarded as standard in adult patients with brainstem lesions.

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Table 1:

Patient characteristics	No.
Median age (years)	43
Age range	18-78
Male/female	25/21
Median duration of symptoms (weeks)	40 (1 – 360)
Median survival (mths)	28 (1 – 91)
Median F/U (mths)	17 (1-91)

Baseline characteristics of patients enrolled.

*Table 2:***Radiologically suspected brainstem glioma (WHO I°-IV°)**

Histology	No.
Pilocytic astrocytoma (WHO I°)	2
Low grade astrocytoma (WHO II°)	14
Anaplastic astrocytoma (WHO III°)	8
Glioblastoma multiforme (WHO IV°)	4
Metastasis	7
Lymphoma	5
Inflammation	2
Cavernoma	1
No tumor/gliosis	3

Histological results in 46 patients with radiologically suspected „glioma“ in the brainstem. In 28 /46 patients radiological diagnosis could be confirmed by histology.

Table 3:

Radiologically suspected low grade gliomas (WHO I° & II°)

Histology	No.
Pilocytic astrocytoma	1
Low grade astrocytoma II°	6
Anaplastic astrocytoma III°	4
Glioblastoma multiforme	3
Lymphoma	2
Inflammation	2
No tumor/gliosis	1
Cavernoma	1
Metastasis	6

Histological diagnosis in the subgroup of patients with suspected low grade glioma. In 7 out of 26 patients tissue diagnosis met radiological assessment.

Table 4:

Radiologically suspected high grade gliomas (WHO III° & IV°)

Histology	No.
Pilocytic astrocytoma (WHO I°)	1
Low grade astrocytoma (WHO II°)	6
Anaplastic astrocytoma (WHO III°)	5
Glioblastoma multiforme (WHO IV°)	2
Lymphoma	3
No tumor/gliosis	2
Metastasis	1

Histological diagnosis in the subgroup of patients with radiologically suspected high grade glioma. Seven out of 20 patients showed high grade glioma in histological workup.

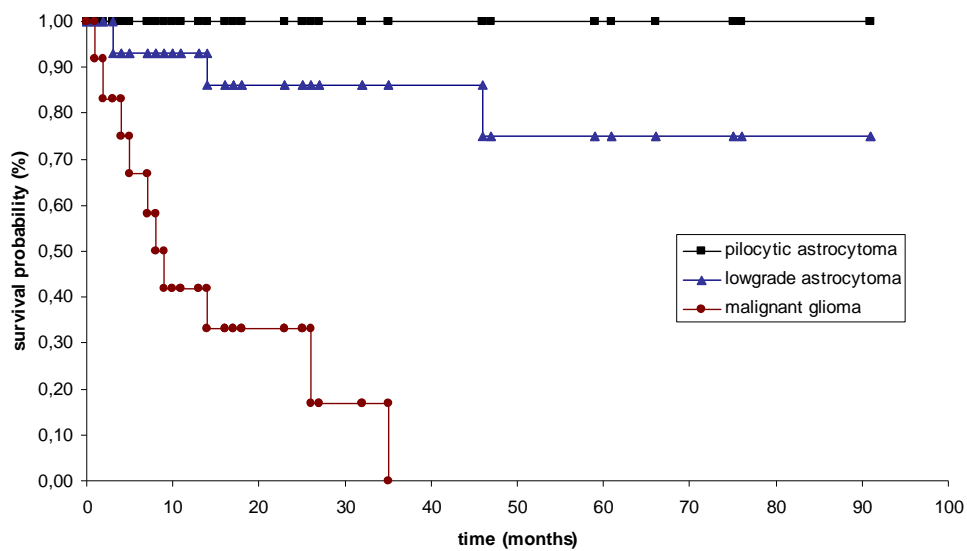
Table 5:

Univariate analysis of survival

Candidate covariates	Univariate p-value
diffuse growth pattern	0,96
Extention >1 segment	0,43
higher tumor grade	0,002*
age	0,15
duration of symptoms	0,39
contrast enhancement	0,21
karnofsky performance score (KPS)	0,004*
cranial nerve impairment	0,85

In univariate analysis two prognostic factors (*) reached statistical significance by influence on survival.

Figure 1:



Survival curve for study cohort. Kaplan-Meier was estimated for 46 patients within a 95% two-sided confidence interval.

Image 1:

66 year old, female. Symptoms developed within three weeks: hemiparesis, hemihypesthesia, facial palsy, vertigo. MRI showed contrast enhancing lesion on T1W (A, B) and diffuse hyperintense lesion on T2W (C). Histological workup revealed a high cellular density (D), a high proliferation index (E) and strong immunoreactivity for CD79a (F). Histopathological diagnosis was B-cell lymphoma.

