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Tools and techniques

"Two is not enough" – Impact of the number of tissue samples obtained from stereotactic brain biopsies in suspected glioblastoma

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ABSTRACT

Objective: Stereotactic procedures are performed in many neurosurgical departments in order to obtain tumor tissue from brain lesions for histopathological evaluation. Biopsies can be performed frame-guided and frame less. Some departments use a biopsy needle (cylinder probe), others a forceps for repetitive smaller tissue samples. Although the applied techniques are somehow different, it is still unclear how many tissue samples have to be taken to establish reliably a final diagnosis based on histopathological and genetic examinations. Only precise histopathological diagnosis results in adequate therapy.

Methods: We included 43 consecutive patients who underwent stereotactic biopsy of a suspected glioblastoma between 02/2013 and 07/2015. All patients showed contrast enhancing tumors in the MRI. The patients underwent stereotactic biopsy with the Leksell frame attached to their head. All stereotactic procedures were performed in the presence of a neuropathologist. Target and Entry Points were calculated with BrainLab iplan software (BrainLab iplan 1.0, Munich, Germany). First the two samples 5mm before the Target (pre-target) and the "Targetpoint" itself were analyzed (group 1), then a histopathological evaluation of all samples was performed (group 2).

Results: Mean number of extracted samples was 14. Using classical hematoxylin-eosin stainings, in group 1 histopathological diagnosis was correct in only 30 cases accounting for 73%. Contrariwise a final diagnosis was made in 100% in group 2.

Conclusion: If only two tissue samples were evaluated in this group of patients with suspected glioblastoma, a correct diagnosis was possible in only 73% of the cases. We conclude that two samples are not enough to establish a final diagnosis even in a subgroup of suspected glioblastoma.

1. Introduction

In many neurosurgical departments stereotactic procedures are performed on an everyday basis. The indication for this procedure is to obtain tumor tissue from intracerebral lesions in order to perform histopathological and genetic analysis. After neuropathological examination, a final histopathological diagnosis can be established. The final diagnosis is extremely important since further therapy, which often includes chemotherapy and/or irradiation can only be based on correct diagnosis. The procedure is generally performed with high safety and precision resulting in high diagnostic yield. Also deep seated tumors and lesions in eloquent areas can be reached safely and in most of the case series published, a final diagnosis could be established [13,15].

In our already published studies we have shown, that the procedure can be performed safely not only in adults but also in children, HIV patients, and patients with brainstem lesion as well as pineal lesions. Often we were confronted with the question why such a high median number of 12 tissue samples were taken throughout the procedure. Our specimens were taken with a biopsy forceps, resulting in samples of 1 mm size. The reviewers considered two samples to be enough, although there is no reference in the literature stating how many samples are needed. In this

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study we evaluate whether this is true and if taking only two tissue samples will lead reliably to a conclusive final diagnosis (Fig. 1).

2. Patients and methods

2.1. Patient inclusion

We prospectively recruited patients who were admitted to the department of neurology and neurosurgery at the University hospital, Frankfurt/Main, Germany between February 2013 and July 2015. All included patients showed a contrast enhancing lesion being suspicious of glioblastoma in conventional MRI and received a stereotactic biopsy to establish a histological diagnosis. All patients underwent thin-slice MR imaging for stereotactic planning. Patients with other contrast enhancing lesions in the MRI not suspicious for glioblastoma like lymphoma, chronic inflammatory CNS lesions, etc. were excluded.

The study protocol (04/09) was approved by the local ethics committee of the University hospital of the Goethe University Frankfurt/Main, Germany. All patients who attended in the study gave their written informed consent.

2.2. Surgical procedure

The stereotactic frame (Leksell) was attached to the patients' head prior to surgery. The frame was fixed with two screws frontal and two screws occipital. All patients underwent the procedure under general anesthesia.

In the next step, a CT scan was performed. This scan with the attached frame was then fused to the MR imaging. The trajectory with entry and targetpoint was calculated using BrainLab iplan system (BrainLab iplan 1.0, Munich, Germany) (Fig. 2).

The stereotactic frame was then adjusted to the calculated coordinates of the trajectories.

After a burr hole was performed, tissue probes were taken in 1 mm steps with a biopsy forceps.

All tissue specimens were handed to the neuropathologist, who was present during every procedure. A minimum of one smear preparation was performed during the stereotactic biopsy to guarantee, that pathological tissue changes was present. Postoperative CT scans were not performed on a routine basis.

2.3. Sample selection

First we analyzed only two samples of each patient (group 1). These tissue samples were taken from position −5 (5mm before target point – called pre-target) and the target point itself. In a second step we analyzed all samples using histochemistry and immunohistochemistry also including antibodies against ATRX, mutated IDH1R132H, mutated H3K27M (group 2).

3. Results

43 patients were included in this study (25 male, 18 female, age range: 26–88 years, mean age ± SD: 63 ± 13 years)

By analyzing only two samples (group 1) 27 patients received the diagnosis of a glioblastoma, in eight patients the diagnosis of a diffuse glioma was made, in three that of an anaplastic astrocytoma, a cerebral metastasis of a carcinoma was diagnosed in two patients and in three cases only necrosis was found (Table 1). By analyzing all samples (group 2) the suspected diagnosis of a glioblastoma was confirmed in 37 patients by neuropathological examination, six patients had another diagnosis. In detail, one patient had a diffuse glioma, three an anaplastic astrocytoma and two patients had a cerebral metastasis of a carcinoma (Table 2).

4. Discussion

Since stereotactic procedures are performed in numerous neurosurgical departments for the past decades [12,16], studies have analyzed almost every aspect of the procedure. Procedures were evaluated concerning the modality of anesthesia used (general versus local) [10,18,19], the localization of the biopsied lesion [11,12], hemorrhage rates, postoperative imaging [2], patient age [3,10,14], diagnostic yield [4,5,20] and frame-based versus frame-less procedures [9,17]. Even robot-assisted procedures have lately been evaluated, showing a high diagnostic yield with a low complication rate [7].

Also imaging techniques have improved over the last decades, especially focusing on tumor metabolism. This information helps the surgeon to plan targets in areas of high tumor activity [1,8]. Nevertheless biopsy and subsequent histopathological and molecular analysis remains the mainstay of diagnosis. Inconclusive biopsies are often due to mere necrosis in the biopsy sample [4]. Thus, in order to gain specimens with a maximum of tumor cells (about 70% tumor cells are needed by the pathologists), the target point should be set in the contrast enhancing area of the tumor. The trajectory should be planned in a tangential manner to get samples with a maximum of tumor cells [20].

Several biopsy tools are available today. Mostly a biopsy needle or a biopsy forceps are used. Advantage of the biopsy needle might be that no single specimens, but a tissue-cylinder is cut out [5]. By using a forceps only very small probes are taken, but the procedure using the forceps goes in hand with a maximum of safety, since the branches are not cutting [6]. Also new techniques have been developed to gain higher diagnostic yield e.g. combination of needle-aspiration and core needle biopsy as shown by Hirschfeld et al. [5].

There is no consensus how many tissue specimen are necessary to establish a final diagnosis. Jain et al. have shown that a higher number of tissue samples correlated with a higher diagnostic yield but they only took a maximum of six tissue samples [6]. In the study at present we could show on the one hand that by analyzing only two samples in a selected subgroup of patients with suspected glioblastoma a conclusive diagnosis was feasible in only 73% of the cases. While diffuse gliomas and metastasis were correctly diagnosed in all cases, it was more difficult to diagnose glioblastoma on basis of two tissue samples only. All anaplastic astrocytomas were completely misdiagnosed as diffuse gliomas. If this applies for the here mentioned subgroup of tumors, the rate of incorrect diagnosis must be even higher if patients with all kinds of brain lesions (not only suspected glioblastoma) were evaluated. Our findings underline that two probes war definitively not enough and emphasize the necessity to take more tissue samples. In doing so, we could show on the other hand that with a median of 14 samples a conclusive diagnosis was possible in all patients being tantamount to a diagnostic accuracy of 100%.

5. Conclusion

Even in patients with the typical appearance of glioblastoma in imaging two tissue samples are not enough to confirm this diagnosis reliably. Hence a significantly higher number of samples must be taken to make a conclusive diagnosis since only exact diagnosis can result in adequate further therapy.

Conflicts of interest disclosure

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock

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