Stereotactic biopsy in elderly patients: risk assessment and impact on treatment decision

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Abstract To evaluate risk profile, diagnostic yield and impact on treatment decision of stereotactic biopsy (SB) in elderly patients with unclear cerebral lesions. In this single center retrospective analysis we identified all patients aged ≥70 years receiving SB between January 2005 and December 2015. Demographic data, Karnofsky Performance Status (KPS), histology, comorbidity (by CHA2DS2-VASc Score) and use of anticoagulation were retrieved. We scrutinized diagnostic yield, procedural complications (mortality, transient and permanent morbidity), hospitalization time and therapeutic consequence. For correlation analysis Chi-Square, Mann–Whitney rank sum test and binary regression were used. Two hundred and thirty patients were included. In 229 patients SB was technically successful. Median age was 74 (70–87) years, 56.1% of patients were male and median preoperative KPS was 80% (30–100). Median CHA2DS2-VASc Score was 4 (1–9), with 29.6% receiving anticoagulation. Median hospital stay was 8 (2–29) days. Pathological diagnosis was conclusive in 97% revealing neoplastic lesions in 91.7% (high-grade glioma 62.6%, lymphoma 18.3%, metastasis 4.8%, low-grade glioma 3.0% and other tumors 3.0%) and non-neoplastic lesions in 5.3% of cases. Procedure-related mortality was 0.4%, transient and permanent morbidity occurred in 19 patients (8.3%) and eight patients (3.5%). Complication rate was not associated with any of the above-mentioned parameters. Adjuvant therapy was initiated in 171 (74.3%) patients. Decision against disease-specific therapy was only influenced by preoperative KPS (p < 0.001). SB in elderly patients is characterized by a favorable risk profile and high diagnostic yield, allowing tissue based therapeutic consequences even in patients with high comorbidity and anticoagulant medication.

Keywords Neurooncology · Stereotactic biopsy · Elderly

Abbreviations
GBM Glioblastoma multiforme
KPS Karnofsky Performance Status
MRI Magnetic resonance imaging
SB Stereotactic biopsy
WHO World Health Organization

Introduction

Molecular markers allow for more precise tumor classification and disease-specific therapy according to the NOA08 trial and the latest WHO classification of tumors of the central nervous system [1, 2]. Thus obtaining tissue for exact neuropathological diagnosis by either resection or SB is advisable, especially with malignant gliomas appearing most frequently in the elderly, and with regard to the main differential diagnosis of primary brain lymphomas [3, 4].

While in younger patients striving to confirm diagnosis is almost self-evident, for patients aged 70 years or older surgery in general is more critically discussed due to an assumed higher risk profile.
This assumption is derived from data describing the risk profile of brain tumor resection in patients over 70 years showing a complication rate of up to 20% [5, 6]. The professed association between age and complication rate also seems to be expected for stereotactic biopsy (SB) in elderly patients, leading towards different therapy options, such as primary radiotherapy or supportive care, in the case of an assumed malignant tumor.

Since no data from larger cohorts exist to evaluate the complication profile for SB in the elderly population, the specific aim of this study was to re-evaluate risk assessment and the impact on treatment decision of performing SB in elderly patients with unclear cerebral lesions.

Clinical material and methods

Patient population

In this single-center study a consecutive series of patients aged 70 years or older with unclear cerebral lesions undergoing SB between January 2005 and December 2015 was identified. The decision for performing SB was made within an interdisciplinary neuro-oncology board. SB was considered, if the patient presented in a good neurological condition or if morphological imaging implicated cerebral lymphoma, with a potential for rapid improvement after administration of steroids.

The patient’s medical history was analyzed for age, gender, preoperative KPS, length of hospital stay, use of anticoagulant medication as well as co-morbidities. The CHA2DS2-VASc Score, with a range from 0 to 9 points, was originally developed for predicting stroke and thromboembolism in patients with atrial fibrillation and is related to the use of anticoagulant medication [7]. Since this score includes the most important cardiovascular diseases and latest data suggest it to be a risk-stratification tool for predicting adverse clinical events independent from atrial fibrillation [8], we chose the CHA2DS2-VASc Score to assess co-morbidity. Diagnostic yield of SB, tumor localization, histology and procedural complications were evaluated. Morbidity was defined as transient if newly occurring or aggravated symptoms resolved within 30 days, and otherwise defined as permanent. The therapeutic consequence of SB, meaning any kind of initiated disease-specific therapy was investigated.

This retrospective study was approved by the institute’s ethical committee (application number 16-477).

Treatment planning and surgical technique

Surgical procedure was performed as previously published and anticoagulant medication was adequately suspended [9, 10]. All biopsies were performed by experienced stereotactic neurosurgeons. In summary, under general anesthesia the patient’s head was fixed using a modified Riechert–Mundinger stereotactic frame, computer-assisted tomography was carried out and co-registered with a previously performed axial T1-, T2-weighted MRI [11]. Specific software was used (STP3, Stryker Leibinger, Freiburg, Germany) for fusion and for trajectory planning and according to the established coordinates the SB device was installed on the stereotactic frame. After skin incision an 8 mm burr-hole was set using a twist drill and dura mater was incised. A Backlund biopsy needle was introduced following the trajectory throughout the lesion and a tissue specimen was taken for definitive histopathology, immuno- and molecular diagnosis, as well as to generate frozen sections for intraoperative evaluation.

Statistical analysis

Statistical calculations were carried out using SPSS version 22 software (SPSS Inc., Chicago, IL). Wilcoxon rank sum test for nonparametric data and Chi-Square test for categorical variables were performed. Univariate analysis was performed to identify covariates that influence the complication rate and affect therapeutic decision using binary logistic regression. Therefore the following parameters were analyzed: gender, age, preoperative KPS, localization of lesion, CHA2DS2-VASc Score, anticoagulant medication. Data are shown as median with a p-value of less than 0.05 regarded as significant.

Results

Patient population

In the defined period 239 patients were identified, of whom 230 patients with complete data records were included in the analysis. Patient’s baseline characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tbody>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Median (range)</td>
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<tr>
<td>%</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>KPS, index in %</td>
</tr>
<tr>
<td>CHA2DS2-VASc Score, points</td>
</tr>
<tr>
<td>Time as in-patient, days</td>
</tr>
</tbody>
</table>

KPS Karnofsky Performance Score
The median age was 74 years, ranging from 70 up to 87 years; 56.1% of the patients were male. The median preoperative performance status was 80% (range 30–100).

The cohort showed a high co-morbidity rate with a median CHA2DS2-VASc Score of 4 points; 29.6% were receiving anticoagulant medication or platelet aggregation inhibitors, which were suspended about 7 days preoperatively. Median time as an in-patient was 8 days (range 2–29).

Localization of lesions can be seen in Table 2.

Histopathological diagnosis revealed neoplasms in 91.7% of cases, with high grade gliomas being the leading diagnosis (62.6%). Other results were lymphoma (18.3%), metastasis (4.8%), low-grade gliomas (3.0%) as well as other tumors (3.0%). Non-neoplastic lesions were detected in 5.3% and histopathology was inconclusive in 3% of patients.

Risk profile and therapeutic consequence

SB was performed successfully in 229 cases (99.6%). In one case the procedure was interrupted in the planning phase, since due to a highly vascularized tumor, no acceptable trajectory could be established.

Mortality rate was 0.4%, one patient died from intracerebral hemorrhage. Overall morbidity was 11.8% with transient morbidity in 19 patients (8.3%) and permanent morbidity in eight patients (3.5%). Of the latter, seven patients showed an aggravation of preoperative symptoms, e.g. deterioration of pre-existing hemiparesis, and one patient with an extended primary central nervous system lymphoma developed a decrease in consciousness that did not recover within 10 days. Adjuvant disease specific therapy was initiated in 171 patients (74.3%).

Table 2  Localization of cerebral lesions

<table>
<thead>
<tr>
<th>Localization</th>
<th>%</th>
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<tbody>
<tr>
<td>Supratentorial</td>
<td></td>
</tr>
<tr>
<td>Non-eloquent/lobar areas</td>
<td>60.4</td>
</tr>
<tr>
<td>Midline structures</td>
<td>23.9</td>
</tr>
<tr>
<td>Eloquent areas</td>
<td>8.7</td>
</tr>
<tr>
<td>Infratentorial</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>1.8</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Subcortical midline structures include corpus callosum, sella, pineal region, basal ganglia, thalamus, internal capsule and brainstem. Eloquent areas were defined as sensorimotor and language cortex as well as the primary visual cortex. Non-eloquent areas comprise the remaining lobar regions.

Predictor for morbidity or adjuvant therapy

In univariate analysis no association between complication rate and age, pre-existing diseases or anticoagulant medication was found. The rate of adjuvant treatment was significantly higher in patients with a KPS >70 than in patients with a score less than 70 (p <0.001).

Discussion

According to recent data the incidence rate for brain tumors rises rapidly among patients aged over 65 years, especially regarding the main malignant diagnosis of glioblastoma multiforme (GBM) [12].

To establish a definite diagnosis, obtaining tissue either by open surgery or by SB remains the gold standard. This, however, seems to be more a subject of debate in this frail cohort due to an assumed higher risk profile, with the result of constraining offering this important diagnostic/therapeutic option to older patients compared to patients of a younger age.

Yet data from larger cohorts recording procedure-related complication rates in patients aged over 70 years for SB as well as for microsurgical resection are scarce. D’Amico et al. reported an overall complication rate of 21.4% in 243 patients with a mean age of 73 years after resection of glioblastoma, and concluded that this population is exposed to a greater perioperative risk associated with ageing [6]. Tanaka et al. demonstrated a complication rate of 19% in a cohort of 53 elderly patients (mean age 74 years) after microsurgical resection of newly diagnosed GBM, with neurological complications in 6 patients that were persistent in two cases [5]. For another group of 52 patients undergoing SB the same authors reported an even higher rate of 31% and a mortality rate of 8%.

Analyzing reported results for SB only, Kelly et al. described a series of 88 patients with an average age of 72 years (range 65–83 years) undergoing SB, of whom three patients suffered from postoperative hematoma, which led to the death of two patients (mortality rate of 2.3%) [13]. Muacevic et al. described a transient morbidity of 1.5% and mortality rate of 1.5% in a subgroup of 65 patients with a median age of 62 years undergoing SB and radiotherapy in a subgroup of elderly patients with de novo GBM [14].

Our reported data address risk profile, diagnostic yield and the impact upon treatment decision of SB in a unique series of 229 elderly patients over 70 years of age with unclear cerebral lesions, of whom 79% displayed an independent functional status with KPS ≥70% at the time of SB.

A self-dependent status (KPS ≥70) in 79% of our patients on the one hand and a median CHA2DS2-VASc
Score of 4 points representing a high rate of treatment relevant co-morbidities on the other hand might demonstrate the fragility of this cohort. Whether this combination of characteristics may represent a lower reserve capacity with a consecutive earlier decompensation leading to more complications, as reported especially from patients after microsurgical resection, can only be postulated.

Analyzing the procedure-related complications after SB in our cohort, we found a mortality and transient complication rate of 0.4 and 8.3%, respectively, while permanent morbidity occurred in 3.5% of patients. When putting these results in context with reports from patients of all ages undergoing SB for unclear brain lesions, our permanent complication rate lies at the upper limit within the range (Table 3). The higher rate of transient morbidity, which is not reported in detail by the other authors, might be explained by our narrow definition of any deterioration or symptom being reversible within the relatively short period of 30 days.

One central finding of our data is that the detected procedural complication rate is neither associated with increased age (≥70 vs. ≥75 years) or preoperative KPS (<70 vs. ≥70%), nor comorbidities (CHA2DS2-VASc Score of <4 vs. ≥4 points.) or localization of the lesion (lobar vs. midline). This finding also holds true for the anticoagulant medication used—when adequately paused—which is not associated with higher risk for i.e. postoperative hemorrhage.

Other SB databases detected neoplastic lesions in 80 and 83% with a proportion of 45% malignant gliomas of WHO Grade III and IV in younger patients with median age of 51 and 49 years, respectively [15, 19]. We found neoplasms in 91.2% of cases, with 62.6% malignant gliomas and 18.3% primary CNS lymphomas, confirming the higher incidence of malignant tumors in elderly patients.

The synopsis shows that SB provided for elderly patients has an acceptable risk profile with a slightly higher morbidity compared to younger patients. Whether experience when performing SB routinely has an influence, as shown by Kickingeder et al. in a meta-analysis of SB for brainstem tumors, cannot be proven by our data [21].

Furthermore, we were able to show that SB in elderly patients enables reasonable therapeutic measures, as 74% of the patients consequently received disease-specific therapy. A highly significant parameter associated with initiation of adjuvant treatment was an independent functional preoperative status (KPS ≥70%) at the time of SB. However, in one case with a preoperative KPS of 50% due to a severe hemiparesis, SB was performed confirming the suspected diagnosis of lymphoma. This patient rapidly improved after the administration of steroids and successfully underwent radiochemotherapy. In contrast, another patient with a suspected cerebral lymphoma, proven by SB, displaying a KPS of 30 due to impaired consciousness did not improve and received supportive care. Thus, also in patients with poor general condition the decision for SB should be carefully considered and decided individually.

Aiming at the rising incidence of malignant gliomas in patients with higher age and the desire to identify the optimal treatment regimes for patients beyond 65 years, two prospective randomized trials were conducted: (i) the NOA-08, and (ii) the Nordic trial [1, 22]. Both studies have demonstrated that adjuvant treatment with either temozolomide or radiotherapy only shows good clinical response in those patients diagnosed with glioblastoma multiforme. Here, the evaluation of immunological and molecular features, such as O(6)-methylguanine-DNA methyltransferase (MGMT)-promoter methylation and isocitrate dehydrogenase (IDH)1 mutational status obtained from tissue by resection or biopsy, represented the basis for decision- and prognosis-making, since the groups were stratified by these markers. Based on our results, this in turn means that the “first” step of obtaining tissue samples is indispensable and will increase the clinical value of SB especially in this cohort due to its demonstrated favorable benefit/risk profile. Nevertheless, further studies are needed to develop geriatric neuro-oncologic guidelines.

Limitations of our study are: (i) a non-excludable selection bias since patients with a poor preoperative functional

<table>
<thead>
<tr>
<th>Author—year (study design) [ref]</th>
<th>n (patients)</th>
<th>Mean age</th>
<th>Permanent morbidity/mortality (%)</th>
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</thead>
<tbody>
<tr>
<td>Field et al. 2001 (retrospective) [15]</td>
<td>500</td>
<td>49</td>
<td>1.6/0.2</td>
</tr>
<tr>
<td>Chen et al. 2009 (retrospective) [16]</td>
<td>299</td>
<td>53.2</td>
<td>2.7/1.3</td>
</tr>
<tr>
<td>Kreth et al. 2001 (prospective) [17]</td>
<td>326</td>
<td>56.8</td>
<td>Overall 2.9/0</td>
</tr>
<tr>
<td>Hall et al. 1998 (retrospective) [18]</td>
<td>134</td>
<td>41</td>
<td>0.7/0.7</td>
</tr>
<tr>
<td>McGirt et al. 2005 (retrospective) [19]</td>
<td>270</td>
<td>51</td>
<td>5/1</td>
</tr>
<tr>
<td>Heper et al. 2005 (prospective) [20]</td>
<td>130</td>
<td>46</td>
<td>0.7/0</td>
</tr>
<tr>
<td>Kellermann et al. 2017 (retrospective)</td>
<td>230</td>
<td>74</td>
<td>3.5/0.4</td>
</tr>
</tbody>
</table>
status are often directed towards supportive care, and not brought to our attention, and (ii) the retrospective study design. In conclusion, SB should not be withheld from elderly patients since the risk profile is acceptable and outweighed by the positive influence on treatment decision towards adjuvant therapy.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

References