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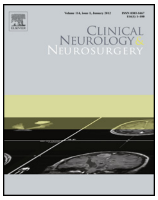

Insular gliomas and the role of intraoperative assistive technologies: Results from a volumetry-based retrospective cohort

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ABSTRACT

Introduction: In the field of Glioma surgery, there has been an increasing interest in the use of assistive technologies to overcome the difficulty of preserving brain function while improving surgical radicality. In most reports, tumor localization has seldom been considered a variable and the role of intraoperative adjuncts is yet to be determined for gliomas of the insula.

Objectives: To evaluate the efficacy of fluorescence-guided resection with 5-ALA, intraoperative neurophysiological monitoring (IOM), neuronavigation, and tractography in the Extent of Resection (EOR), functionality scores, overall survival (OS) and progression-free survival (PFS) in a retrospective cohort of insular gliomas.

Methods: We reviewed all cases of insular tumors operated on at the Department of Neurosurgery, University Hospital of Tübingen – Germany, between May 2008 and November 2013. EOR was determined by volumetric analysis. Mann Whitney, Chi-square and Kaplan Meier functions were used for assessment of each technology's effect on primary and secondary outcomes.

Results: 28 cases (18 men (64%) and 10 women (36%); median age at diagnosis: 52.5 years, range 12 – 59) were considered eligible for analysis. High grade and low grade gliomas accounted for 20 (71%) and 8 (29%) cases, respectively. The most used technologies were IOM (64%) and Neuronavigation (68%). 5-ALA was the only technique associated with EOR $\geq$90% ($p = 0.05$). Tractography determined improvement in the Karnofsky Performance Scale (50% vs. 5% cases improved, $p = 0.02$). There was a positive association between the use of neuronavigation and overall survival (23 vs. 27.4 months, $p = 0.03$), but the use of 5-ALA was associated with shorter OS (34.8 vs. 21.1 months, $p = 0.01$) and PFS (24.4 vs. 11.8, $p = 0.01$).

Conclusions: We demonstrate for the first time that for insular gliomas 5-ALA plays a role in achieving higher EOR, although this technology was associated with poor OS and PFS; also tractography and neuronavigation can be of great importance in the treatment of insular gliomas as they determined better functionality and OS in this study, respectively. Prospective studies with a more prominent sample and proper multivariate analysis will help determine the real benefit of these adjuncts in the setting of insular gliomas.

1. Introduction

The use of novel assistive technologies (ie. intraoperative neurophysiological monitoring, neuronavigation, fluorescence-guided resection and tractography) for intraoperative guidance is a field under continuous debate in the current neurosurgical practice [1–3]. Several studies published to date have addressed the validity of these techniques, but since some technologies require expensive equipment and prolong surgical time, more evidence is necessary to justify widespread use of such adjuncts.

In the field of Glioma surgery, there has been an increasing interest in the use of assistive technologies to overcome the difficulty of preserving brain function while improving surgical radicality. Despite recent reports that some techniques help improve extent of resection and overall survival in Glioma Surgery [4–7], studies' populations are heterogeneous and tumor localization has seldom been considered a variable [8].

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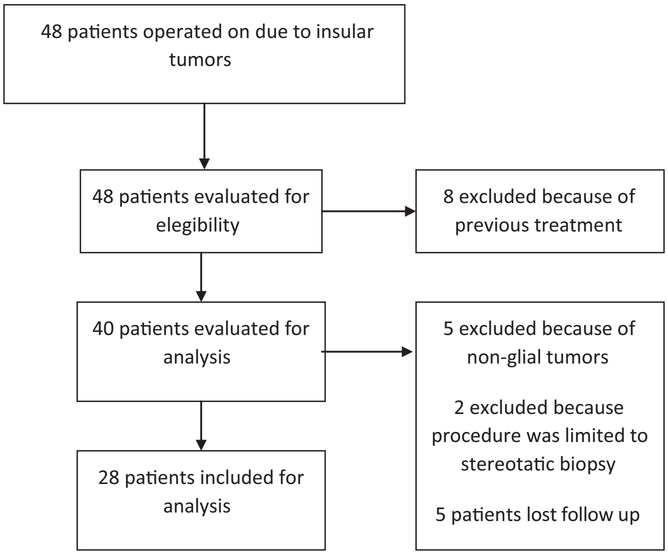

Fig. 1. Flow diagram of patients included in our study.

Due to their deep localization in the Sylvian fissure and complex surrounding structures, insular gliomas have been considered a challenge from the surgical standpoint [9,10]. These tumors are surrounded by eloquent tissue and microvasculature serving critical language and motor systems. Gliomas of the insula account for up to 25% of all low grade gliomas and 10% of all high grade gliomas [11,12]. Standard of care treatment includes maximally safe resection followed by radio-chemotherapy [13]. Although significant improvements have been reported in surgical technique and extent of resection, no major advances have been reached in terms of patients' survival or quality of life. In this scenery, the role of assistive technologies is yet to be determined.

In the present study we aim to evaluate the efficacy of assistive technologies – fluorescence-guided resection, neurophysiological monitoring, neuronavigation and tractography – in the extent of resection (EOR) of insular gliomas. Secondarily, we investigate the impact of these technologies in patients' functionality, overall survival (OS) and progression-free survival (PFS).

2. Methods

2.1. Patient selection

We retrospectively reviewed all 48 cases of insular tumors operated on at the Department of Neurosurgery, University Hospital of Tübingen – Germany, between May 2008 and November 2013. Data were extracted from patients' medical records and plotted in a record form developed for this study (Microsoft Office 2010, Windows 7 version). Medical records provided us with demographic information, tumor characteristics, treatment details – including the assistive technologies used in each case, tumor progression, patients' functionality and death. Patients were considered eligible for the retrospective cohort if they 1) were medically eligible for the surgical procedure; 2) had functionality preserved before surgery with a Karnofsky Performance Scale (KPS) $\geq$70; and 3) had a newly diagnosed glial tumor confirmed by histopathology. Exclusion criteria were 1) presence of multifocal lesions on the preoperative magnetic resonance image; 2) any previous treatment of the insular tumor; 3) a non-glial lesion confirmed by histopathology; 4) if the procedure was limited to tumor biopsy and 5) lack of follow up. Fig. 1 shows patients' flow chart.

2.2. Assistive technologies

In addition to the standard preoperative evaluation with computed tomography (CT) and magnetic resonance imaging (MRI), some patients underwent 3-dimensional tractography based on diffusion tensor imaging (DTI) to reveal the descending motor pathways (8 cases). For intraoperative guidance, some procedures were performed under the assistance of fluorescence with 5-ALA (9 cases), intraoperative neurophysiological monitoring (18 cases) and/or neuronavigation (19 cases). The decision concerning the use of a specific technology took into account the case discussion at the tumor board, the availability of the technique at the department by the time surgery was indicated, technical aspects (tumor location, proximity to eloquent areas etc) and the attending surgeon's experience. In the following paragraphs we briefly describe technical details of the technologies used, in accordance with previous publications by our group [14–17].

2.2.1. Tractography

Data from DTI were acquired along 6 noncollinear gradient directions with an echo-planar imaging sequence of 60 axial slices covering the brain from the pons to the vertex (repetition time, 7300 milliseconds; echo time, 80 milliseconds; flip angle, 90°; b value, 800 s/mm^2; slice thickness, 2.5 mm; gap, none; matrix, 128 × 128 pixels; field of view, 238 × 238). For each individual data set, the normalized eigenvector map, fractional anisotropy map, color map and tensor trace map were calculated with DTILab (NeuroQLab, Fraunhofer Mevis, Bremen, Germany) or MedINRIA 1.5 (INRIA-Asclepios, Sophia Antipolis, France) [15].

2.2.2. Neuronavigation

Imaging data were analyzed offline, loaded into a neuronavigational system and used intraoperatively. A CBYON CBYON Inc, Mountain View, California or BrainLab (BrainLab AG, Feldkirchen, Germany) neuronavigation system was used for preoperative planning and intraoperative navigation [15].

2.2.3. Intraoperative neurophysiological monitoring (IOM)

For IOM, a Nicolet Endeavor CR (Cardinal Health, Dublin, Ireland) was used. Before surgery, bilateral tibial and median nerve somatosensory evoked potentials (SEPs) were elicited by conventional stimulation at the ankle and wrist (25 mA; duration, 0.2 miliseconds; 5.3 Hz) and recorded via scalp corkscrew electrodes placed over the primary sensory cortex. Transcranial motor evoked potentials (MEPs) were elicited with a constant-voltage stimulator (D185, Digitimer Ltd) using corkscrew electrodes placed over the primary motor cortex. Stimulation was performed using 5 pulses of 400–600 V, 50-microsecond pulse duration and an interstimulus interval of 2–4 milliseconds. For the upper limbs, contralateral muscle responses were recorded with needle electrodes inserted in the deltoids, biceps, triceps, wrist flexors and hypothenar and thenar muscles. Responses of the anterior tibial and abductor hallucis muscles in the lower limbs were recorded. Amplitudes and latencies for MEPs and SEPs of the recorded body parts were noted at the beginning and the end of surgery. Measurements of SEPs from the median nerve were based on the peak of the N20 component and SEPs from the tibial nerve on the P40 component. Intraoperative identification of the central sulcus and primary motor area was obtained with a combination of SEP phase reversal and direct monopolar anodal high-frequency electric stimulation of the cortex (5-pulse sequence train; duration, 1 ms; 500 Hz; stepwise increase of stimulation intensity up to 25 mA), with the frontal needle electrode placed at the FZ cathode [18]. The main criterion to stop a resection was the positive localization of either a functional area or a cortical tract in the resection area. Resection was also stopped in case of a