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# Positive influence of partial resection on overall survival of patients with overlapping glioblastomas

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ABSTRACT

*Objectives:* Patients with overlapping glioblastomas (former known as gliomatosis cerebri according to the 2007 WHO classification) have a poor prognosis. Most of the patients undergo biopsy to confirm histopathological diagnosis. Treatment comprises chemotherapy, radiation and combination of both. We determined whether resection of the contrast enhancing tumor parts leads to a prolonged survival.

*Patients and methods:* We performed a retrospective analysis and included 31 patients with overlapping glioblastomas (OG) who showed WHO IV in the initial histopathological examination. All patients fulfilled criteria of overlapping glioblastomas in the MRI according to WHO criteria (3 or more lobes were affected).

We evaluated Karnofsky performance score (KPS), gender, age, IDH-1_R132H status, MGMT promotor methylation status, proliferation index, postoperative therapy, biopsy vs. partial resection and extent of resection as possible factors affecting overall survival (OAS).

A matched pair analysis was performed between the biopsy and resection group on basis of age, KPS and combined radio-chemotherapy.

*Results:* 10 Patients underwent resection of the contrast enhancing tumor parts, 21 patients underwent stereotactic biopsy. All included patients showed contrast enhancing lesions in the MRI.

Median age was 61 years in the biopsy-group and 53 in the partial resection (PR) group. We found a significant correlation between OAS and age $< 50$ ($p = 0.02$). Median KPS was 80 in the STX group vs. 100 in the PR group. KPS above 80 was significantly associated with longer OAS ($p = 0.02$). Median survival was 174 days in the STX group compared to 446 days in the PR group ($p = 0.05$). Also the matched pair analysis showed significant p-values for resection.

*Conclusion:* Partial resection might have a positive impact on overall survival of patients with overlapping glioblastomas (former known as gliomatosis cerebri), although the prognosis remains limited.

## 1. Introduction

Overlapping glioblastomas (OG) (former gliomatosis cerebri, GC) [12,13] is known to be a rare, highly aggressive tumor entity. According to the classification of the WHO 2007 [12]. At least three brain lobes had to be involved to fulfill the criteria of gliomatosis cerebri (GC). Brainstem and basal ganglia are taken as individual lobes according to that classification. GC can either occur as “primary” GC, or “secondary” GC as progression of a glioma. In the new WHO classification gliomatsis cerebri is no longer an own entity but refers to an unusual growth pattern, therefore in this study named overlapping glioblastomas (OG) [13]. The names “overlapping glioblastoma (OG) and gliomatosis cerebri (GC) are used as synonyms in this paper.

In the past, the diagnosis of OG was only made after autopsy, but due to the widespread use of MRI, OG is discovered earlier today [19]. Both, adults as well as children are affected by this devastating disease, although there is a peak between 40 and 50 years and a slightly higher incidence in males. Mostly patients present with headache and seizures as unspecific initial symptom [8]. But depending on localization OG can also cause focal neurological deficits [6,14]. MRI is the imaging of

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choice and usually reveals asymmetrical, hyperintense regions in T2 and partially contrast enhancement in T1 in some patients.

Since the disease is rare, mainly small patient series have been published so far [8,22,14]. Therefore treatment regime is still unclear and ranges from irradiation to different chemotherapeutical regimes and the combination of both [2,3]. Radiation dose usually ranges from 50 to 66 Gy. For chemotherapy mostly PCV (Procarbazine, CCNU, Vincristine) and Temozolomid (TMZ) are used [3,7,10]. Prognostic factors affecting OAS, though, are lacking. There is little known about effects of surgery since in the majority of cases only stereotactic biopsy is performed in order to confirm the diagnosis. In this study we focused especially on the possibly positive prognostic value of resection of the contrast enhancing tumor tissue suspected to be the high grade part of the tumor compared to mere biopsy.

To the authors knowledge this is the first study emphasizing on the effect of resection in this particular group of patients.

## 2. Patients and methods

We performed a retrospective analysis of our prospective data base and included 31 patients with overlapping glioblastomas (WHO IV) who underwent either stereotactic biopsy or partial resection between June 2006 and July 2015. We assessed age, gender, KPS, molecular markers, treatment, localization, and STX versus partial resection (PR) as possible prognostic factors. All patients included in this study fulfilled MRI criteria for OG, meaning that three or more lobes were involved in the MRI.

The study was approved by the local ethics committee.

Evaluation of IDH-1 R132H and the ratio of proliferating cells with the marker Ki67 were performed by immunohistochemistry using DiscoveryXT immunohistochemistry system (Ventana, Strasbourg, France) with standardized protocols as published before. MGMT promoter methylation status was assessed by methylation-specific polymerase chain reaction (MSP).

Pre and postoperative tumor volume (T1 contrast enhancing lesions) of the patients who underwent PR was calculated by using BrainLab software (iPlanCranial 1.0 software; BrainLab system, Feldkirchen/Munich). In one patient only postoperative imaging was archived (no rest tumor was visible)

### 2.1. Radiological findings

All MRI (PR and STX patients, pre- and postoperative) were evaluated by a single, experienced neuroradiologist.

60 Years old patient with first diagnosis of OG (Fig. 1).

#### 2.1.1. Upper and middle row

Initial MRI revealed diffuse areas of voluminous hyperintensities on FLAIR and T2 weighted images of the left cerebral hemisphere including the level of the basal ganglia, the insular region and the left temporal lobe (a and b, ellipse). T1 weighted images in axial orientation ± contrast agent prior to surgery revealed contrast enhancing masses in the cortex of the insular region (c and d, dotted arrow) as well as in the left temporal lobe (g and h, arrow).

#### 2.1.2. Lower row

Postoperative MRI after resection of the enhancing tumor masses of the left temporal lobe with a cystic parenchymal defect with slightly hemorrhages at the periphery of the resection cavity (arrows) on axial T2w/FLAIR images (i and j) and T1 ± contrast agent (k and l) images. Residual contrast enhancing tumor was not obvious (asterisk). Note the remaining T2w hyperintensities of the left temporal lobe adjacent to the resection cavity (Fig. 1). 74 years old male patient with OG (Fig. 2)

#### 2.1.3. Upper row

Initial MRI study performed prior to surgery showed diffuse areas of voluminous hyperintensities in FLAIR/T2 weighted images (a and b; ellipse) involving the temporal lobe, the insular region and the parietal lobe. T1 weighted images ± contrast (c and d) revealed large contrast enhancing mass in the right temporal lobe with adjacent nodular contrast enhancing satellite lesion (arrows).

#### 2.1.4. Lower row

Postoperative MRI, performed after partly resection of the enhancing tumor masses of the right temporal lobe, showed a cystic parenchymal defect with slightly hemorrhages on T2 weighted images (e and f) and remaining T2 w hyperintensities (ellipse). Postsurgical T1w ± contrast (g and h) images revealed residual contrast enhancing tumor adjacent to the parahippocampal gyrus (arrows) (Fig. 2).

### 2.2. Patients' selection for partial resections

Mostly patients with good KPS (70 and above) was offered partial resection if contrast enhancing tumors were localized in non-eloquent areas. In median patients who underwent partial resection were 8 years younger than patients who underwent STX alone (53 years versus 61 years).

### 2.3. Statistical methods

An unpaired *t*-test was used for parametric statistics (age). Categorical dichotomized (DIC) variables were analyzed in contingency tables using the Fisher exact test (IDH1, MGMT negative, combined radio/chemotherapy). Mann-Whitney-U test was used for non-parametric statistics (KPS, Ki67) and the log rank (Mantel-Cox) test for survival analysis. Odds ratio (OR) and 95% confidence interval (CI) were given for categorical variables. Results with a $P$ value $\leq 0.05$ were considered statistically significant. All calculations were made with standard commercial software (IBM SPSS©; IBM Corporation, Armonk, New York, USA).

### 2.4. Matching procedure

For the matched-pair analysis, the statistical computing program R (version 3.0.3; The R Foundation for Statistical Computing, https://www.r-project.org/) was used.

After identifying 10 patients with partially resection, we performed a multivariate and propensity score matching with balance optimization. A total of 10 patients with stereotactic biopsy from the remaining patients were selected (using R) as control group. To improve the balance, the following possible outcome factors (s. Fig. 3) were selected for matching: age, KPS, combined radio-chemotherapy.

## 3. Results

### 3.1. Tumor volumes

Preoperative Tumorvolumes ranged between 9 and 29 $cm^3$ (See Table 1)· Median Tumor volume resected was 26 $cm^3$. Median resection rate was > 90% concerning the contrast enhancing tissue which was planned to be resected. Two patients showed residual tumor which had planned to be resected (3.4 $cm^3$ and 0.88 cm). But also in these two patients > 90% resection rate was achieved.

In three patients contrast enhancing tumor tissue distant to the resection areal was not resected because of eloquent localization. Also in these three patients a > 90% rate of resection was reached for the aimed target volumes. Two of the patients in the partial resected group showed a secondary OG. In the STX-group all patients but one showed primary OG.