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## **Surgery for glioblastomas in the elderly: an ANOCEF trial (CSA)**

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## **Abstract**

**Background:** The role of surgery in the treatment of malignant gliomas in the elderly is unsettled. We conducted a randomized trial that compared tumor surgical resection or biopsy only, both followed by standard therapy, in such patients.

**Patients and methods:** Patients aged  $\geq 70$  years with a KPS  $\geq 50$  presenting with a radiological suspicion of operable glioblastoma (GBM) were randomly assigned between tumor resection and biopsy. Subsequently, they underwent standard radiotherapy during the first years of the trial (2008-2017), with the adjunction of temozolomide when this regimen became standard (2017-2019). The primary end point was survival, and secondary endpoints were progression-free survival (PFS), cognitive status (MMS), autonomy (KPS), quality of life (EORTC QLQ C30 and BN20), and perioperative morbidity/mortality.

**Results:** From 2008 to 2019, 107 patients from 9 centers were enrolled in the study; 101 were evaluable for analysis because a GBM was histologically confirmed (50 in the “surgery” arm/51 in the “biopsy” arm). There was no statistically significant difference in median survival between the “surgery” (9.37 mo) and the “biopsy” arms (8.96 mo,  $p=0.36$ ) and adjusted HR was 0.79 (0.52-1.21,  $p=0.28$ ). However, the surgery group had an increased PFS (5.06 mo vs. 4.02 mo;  $p=0.034$ ) and adjusted HR was 0.52 (0.32-0.78,  $p=0.002$ ). Less deterioration of QOL and KPS score evolution than in the “biopsy” group was observed. Surgery was not associated with increased mortality or morbidity.

**Conclusion:** This study suggests that debulking surgery is safe, and, compared to biopsy, is associated with a less severe deterioration of QOL and autonomy and, a significant although modest improvement of PFS in elderly patients suffering from newly diagnosed malignant glioma. Although resection does not provide a significant survival benefit in the elderly, we believe that the risk/benefit analysis favors an attempt at optimal tumor resection in this population, providing careful preoperative geriatric evaluation.

## **Introduction**

Glioblastoma (GBM) is the most frequent primary brain tumor in adults. Its incidence is increasing in the elderly<sup>1</sup>. Increasing age is one of the most important pejorative prognostic factors for this tumor<sup>2,3</sup>. There is currently no proof of the survival benefit of debulking surgery in the elderly. The only prospective data available come from a small randomized trial<sup>4</sup>, which suggested an advantage of surgery compared to biopsy (median survival of 5.6 months versus 2.8 months). These preliminary data prompted the ANOCEF group to assess the efficacy of tumor resection compared to biopsy in a larger series of elderly GBM patients.

## **Methods**

All patients provided written informed consent before participating. Ethical approval was obtained from the Ethics Board. The study was conducted in conformity with the ethical standards of the Declaration of Helsinki and institutional regulations.

## **Eligibility Criteria**

Patients who were at least 70 years with a Karnofsky Performance Status (KPS) score  $\geq 50\%$  were eligible for the trial if they fulfilled the following criteria: i) brain MRI results strongly suggesting a diagnosis of GBM, ii) lesion considered operable regarding usual neurosurgical criteria defined as a lobar tumor, cortical and subcortical, well limited, without deep infiltration and without involvement of the basal ganglia, with a feasibility of debulking of  $\geq 80\%$  of the mass. Exclusion criteria included MRI contraindications; inoperable lesions; pre-existing severe systemic disease contraindicating anesthesia (ASA score 4 to 5); and prior treatment by radiotherapy or chemotherapy for the lesion.

## **Trial Design**

This was a multi-institutional randomized controlled trial with a 1:1 allocation. Randomization was stratified according to center. After randomization, each participant was biopsied or underwent operation. A clinical evaluation of the tolerance of the procedure was performed on the day after surgery. Once a GBM histological diagnosis confirmation was made, the patient underwent accelerated radiotherapy (40 Gy/15 fractions)<sup>5-6</sup> alone, which was standard treatment until 2017. After this date, Perry et al.<sup>7</sup> established accelerated radiotherapy with concomitant and adjuvant chemotherapy with temozolomide as a new guideline, and patients were treated accordingly. At progression, treatment was left to the investigator choice. Clinical evaluations were performed at baseline and then every month. Toxicities were graded using the Common Terminology Criteria for Adverse Effects (CTCAE), version 4.0. Autonomy was evaluated with the KPS, and cognitive status was quickly screened based on a Mini-Mental Status score (MMS) at baseline and then every month. Radiological evaluations were performed every two months. The patients were followed up until death. Quality of life (EORTC QLQ C30 and BN20) was assessed at baseline and every 2 months after inclusion.

## **Outcomes**

The primary endpoint was overall survival (OS), defined as the time between the surgical procedure and death or last follow-up if the patient was alive at the end of the study.

Secondary endpoints were i) progression-free survival (PFS), defined as the time between the surgical procedure and tumor recurrence or death or last follow-up if the patient was alive and progression free at the end of the study; ii) course of KPS score; iii) course of cognitive status measured by MMS; iv) quality of life (QOL) measured by the EORTC QLQ-C30 and BN-20 scores; and v) adverse events related to surgical procedures, with detailed postoperative morbidity and mortality data.

## **Statistical Analysis**

The expected median OS was 23 weeks in the control group and 39 weeks in the surgery group. To detect this difference with a 80% power and a 5% significance level, an accrual of 45 patients per year for 3 years and a group-sequential analysis, a maximum sample size of 135 participants was needed. To compare the two arms OS, a log-rank statistic was used within a sequential-design framework with stopping rules based on triangular test<sup>8</sup> allowing for early stopping study for efficacy or futility at each interim analysis.

Categorical variables were described as frequencies and percentages and continuous variables as means and standard deviations or medians and interquartile ranges. Chi-square test or Fisher's exact test were used to compare categorical variables and Student's test or Wilcoxon's rank-sum test for quantitative variables. OS and PFS were estimated using the Kaplan-Meier estimator and compared using log-rank tests.

Analyses were performed in a modified intention-to-treat population, excluding patients without histologically confirmed GBM.

Baseline risk factors for death and progression were determined using Cox proportional hazard model regression. Factors included in the multivariate analysis were treatment group, sex, age and KPS. Hazard ratios were reported with their 95% confidence intervals.

The changes over time for the QLQC30, BN-20 and MMS scales in the treatment groups were compared by a linear mixed effect model for repeated data. KPS changes over time in the treatment groups were compared by a mixed effect proportional odds model for ordinal repeated

data. The terms introduced in these models were the treatment group, the time in months, and the time x group interaction.

All analyses were performed at a two-sided  $\alpha$  level of 5%, using PEST, version 4.3 (MPS Research Unit, University of Reading) for interim analyses and R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for all other analyses.

## **Results**

### **Patients**

From March 2008 to April 2019, a total of 107 patients from 9 centers were enrolled and randomized to either resection surgery (“S”) or biopsy (“B”) groups. In six patients, histological analysis did not confirm the diagnosis of GBM (metastasis n=2; lower-grade glioma n=1; unclassified tumor n=1; isolated necrosis n=1; hematoma n=1), leaving 101 patients evaluable for modified ITT analysis, 50 in the S group and 51 in the B group [**Flowchart**].

The recruitment was stopped for futility after the fifth interim analysis (in July 2019), in agreement with the decision rules pre-specified in the study protocol.

The baseline characteristics of the 101 evaluable patients are recapitulated by treatment arm in **Table 1**. Participants were aged between 70 and 91 years (median of 78 years in the S arm, 77 years in the B arm). The initial KPS score ranged from 50 to 100, and 18 (36%) patients had a KPS score < 70 in the S arm versus 14 (28%) in the B arm.

### **Treatments**

Ninety-seven (96%) patients were treated according to their randomization arm. Two patients (4%) randomized in the S arm were in fact biopsied, and conversely, 2 patients (4%) randomized in the B arm were in fact treated by partial surgical resection. In the 48 patients

randomized and treated in the S arm, gross total resection (GTR) was performed in 33 (69% of cases) and partial resection was performed in 15 (31% of cases) patients [Table 2].

After the initial procedure, 81 (80%) patients were treated with radiotherapy, and 40 patients (80%) and 41 patients (80%) were treated in the S and B arms, respectively. Depending on the year of treatment (before/after 2017), radiotherapy was delivered alone for 70 patients or by the association of radiotherapy with concomitant and adjuvant temozolomide in 9 patients. Treatment administered to the 82 remaining patients at progression was mostly temozolomide in 47 patients (57%), including 23 patients (56%) in the S arm and 24 patients (59%) in the B arm. Twenty-three patients (28%) received palliative care alone, including 9 patients (22%) in the S arm and 14 patients (34%) in the B arm.

### **Postoperative complications**

An adverse event was reported in 1 patient (2%) during surgery in the S arm and 3 patients (6%) during biopsy in the B arm, but none justified interruption of the neurosurgical procedure [Table 2].

In the immediate postoperative period, there was no significant discrepancy in the complication rate between the arms (16 cases (32%) in the S arm and 13 cases (25%) in the B arm,  $p=0.47$ ). The main complications were cerebral infection in 2 cases (2%), both described in arm B, brain bleeding (4 cases (4%) with 2 cases in both arms), and motor impairment (12 cases (12%), including 5 in the S arm and 7 in the B arm;  $p=0.56$ ). The incidence of other postoperative complications (aphasia, confusion, seizure, headaches, cardiac infarction, pulmonary infection, pulmonary embolism, etc.) was very low (1-4%). Taken together, surgical resection was not associated with greater immediate postoperative mortality or morbidity than biopsy.

### **Primary outcome (overall survival)**



The median follow-up was 40 months. There was no statistically significant discrepancy regarding OS between the S and B arms, with a median survival of 9.37 versus 8.96 months in the S and B arms, respectively ( $p=0.36$ ) [**Figure 1**]. Adjustment for major prognostic factors (age, sex and KPS) in a Cox proportional hazard multivariate model did not change the results ( $HR=0.79$ , 95% CI 0.52-1.21,  $p=0.28$ ). In the multivariate analysis, the unique factor significantly associated with the worst OS was  $KPS<70$  ( $HR=1.72$ , 95% CI 1.05-2.81,  $p=0.03$ ) [**Table 3**]. Post hoc sensitivity analyses excluding patients who had partial resection on one side or were treated with temozolomide on the other side did not affect the results.

### **Progression-free survival**

PFS was longer in patients undergoing resection surgery than in patients undergoing biopsy (median PFS 5.06 vs. 4.02 months,  $p=0.034$ ). The 6-month PFS rate was 41% in the S arm versus 20% in the B arm [**Figure 2**]. After adjustment for prognostic factors, resection surgery was associated with a longer PFS ( $HR=0.50$ , 0.32-0.78,  $p=0.002$ ), and  $KPS<70$  was associated with a shorter PFS ( $HR=2.18$ , 1.34-3.53  $p=0.002$ ) [**Table 4**]. Post hoc sensitivity analyses excluding patients who received partial resection confirmed these results ( $HR=0.39$ , 0.23–0.67,  $p=0.001$ ).

### **Quality of life**

Surgical debulking was associated with a significantly better outcome in terms of QOL than biopsy alone.

The EORTC QLQ C30 scale showed a difference between the S and B arms for each month of follow-up. For example, the mean variation of the physical functioning scale was -0.94 (95% CI -1.242- -0.628) and -0.38 (95% CI) by month in the B and S arms, respectively ( $p=0.014$ ). QOL evolution was also significantly better in the S group for the following items: role

functioning ( $p=0.008$ ), cognitive functioning ( $p=0.01$ ), fatigue ( $p=0.005$ ), nausea and vomiting ( $p=0.044$ ), and appetite loss ( $p=0.007$ ).

Regarding brain tumor-specific items (BN20), the difference in the mean score for each month of follow-up was also significantly better in the S group for the following subscores: future uncertainty ( $p=0.04$ ), motor dysfunction ( $p<0.001$ ), communication deficit ( $p=0.025$ ), weakness of legs ( $p<0.001$ ), and bladder control ( $p<0.001$ ). There was no significant impact on other components.

### **Karnofsky performance status**

An improvement in KPS scores was observed for each month of follow-up in the S arm compared with the B arm (OR=1.19, CI95% 1.09-1.29,  $p<0.001$ ).

### **Neurocognitive functioning**

No significant discrepancy in the evolution of the mean MMS score over time was found between the groups (mean variation by month: -0.3, CI 95% -0.47- -0.13 in the B arm, -0.08, CI95% -0.26-0.1 in the S arm, difference: 0.22, CI95% -0.02-0.46,  $p=0.076$ ).

### **Discussion**

This prospective randomized study suggests that tumor resection is well tolerated but does not meet our predefined primary outcome, failing to show an improvement in survival compared with biopsy in elderly GBM patients treated with postoperative radiotherapy plus or minus temozolomide. Nevertheless, tumor resection improves PFS, performance status and QOL in this frail population.

As in younger patients, there is a consensus on the need to obtain histologic proof of the diagnosis in elderly patients. Despite a sophisticated radiological work-up, a definitive

diagnosis of gliomas needs analysis of a tumor sample collected during surgical resection or by biopsy. Our study emphasizes this point since a diagnosis other than GBM was demonstrated after anatomopathological examination in 6/107 patients (5.6%), a finding in agreement with previous reports<sup>4</sup>.

The role of tumor resection in the elderly remains debated in terms of tolerance and survival benefit. Some authors have underlined the higher risk of postoperative neurologic or systemic deterioration in older patients<sup>9,10</sup>, but recent studies indicate that improvements of surgical and anesthesia techniques have considerably reduced the postoperative risk in the elderly to a level comparable to the younger population<sup>11,12,13</sup>, providing a preoperative evaluation of frailty. In our study, the operative risk was evaluated with the ASA scale, and surgery was considered in patients with an ASA score <4.

In this setting, we found that the rate of postoperative complications (16/50, 32%) did not differ from that observed in the biopsy arm (13/51, 25%). In the literature, a deterioration of the NIHSS score by  $\geq 1$  point was found at 7 days after surgery in 39.1% of patients with EOR  $\geq 80\%$  compared with 16.7% for patients with EOR <80% ( $P=0.0049$ )<sup>14</sup>. The morbidity rate in younger patients is difficult to estimate according to the literature. Indeed, most studies include heterogeneous populations of gliomas. The perioperative complication rate is estimated to be approximately 19.4% of patients<sup>15</sup>. In some series, almost 30% of patients had a new postoperative neurological deficiency (motor weakness, sensory deficits, visual deficits, language impairment, confusion, and ataxia), which subsequently resolved in 41% of cases<sup>16</sup>. Moreover, we did not find a higher rate of postoperative complications in patients undergoing resection than in those undergoing biopsy, suggesting that GBM resection can be safely performed in the older population.

In younger patients, the favorable effect of GBM resection on survival is well acknowledged. This does not rely on prospective randomized trials but on the accumulation of retrospective

and nonrandomized prospective analyses, particularly recent studies that strongly support the survival benefit of tumor resection, ideally GTR. In the elderly, the impact of tumor resection on survival remains more debated despite encouraging retrospective data<sup>17,18,19,20,21,22,23,24</sup> and one small randomized study<sup>4</sup>. A meta-analysis<sup>20</sup> of 34 studies among 12607 patients > 60 years suffering from high-grade glioma found an OS of 5.71 months (95% CI 5.04–6.36), 8.68 months (95% CI 7.87–9.48) and 14.04 months (95% CI 12.8–15.2) in patients undergoing biopsy, subtotal resection and GTR, respectively. Patients undergoing surgical resection (of any extent) had a significant benefit compared with those biopsied, with a mean difference in OS of 3.88 months (95% CI 2.14–5.62,  $p < 0.001$ ). The mean difference was 10.4 (95% CI 6.58–14.22,  $p < 0.001$ ) and 2.44 months (95% CI 1.45–3.43,  $p < 0.001$ ) for postoperative KPS and PFS respectively. Altogether, the analysis revealed a longer survival time, postponed tumor progression rate and better functional recovery with decreasing tendencies in mortality and morbidity rates, suggesting a progressive gain in outcomes with greater degrees of resection. Furthermore, in a small randomized Finnish trial, 23 patients > 65 years with malignant glioma (83% GBM) were accrued. Improved survival was described in patients treated with surgical resection followed by radiotherapy (5.6 months) compared with those treated with biopsy followed by radiotherapy (2.8,  $p=0.035$ ). Resection was also associated with a better QOL<sup>4</sup>. In our study, we could not demonstrate a significant effect of tumor resection on OS. A lack of power cannot be excluded, however the observed difference in overall survival is particularly small between the two groups (9.37 months of median survival in surgery arm and 8.96 months in median survival in biopsy group). Resection encompasses partial, subtotal and GTR. A clear benefit in patients undergoing GTR remains possible, but we could not identify it. Conversely, tumor resection improved PFS, performance status and QOL, all of which are critical in this population.

Our study has several important limitations. Patient accrual was difficult and slow. The extent of resection was not systematically evaluated by early postoperative MRI, requiring great caution to analyze this factor. Data regarding tumor lobar location were also lacking. As a consequence of the long duration of the inclusion phase, the standard postoperative regimen changed during the study (from radiotherapy alone to radiotherapy with concomitant and adjuvant temozolomide). However, a sensitivity analysis was realized excluding patients treated with temozolomide, and the OS and PFS results did not change. Moreover, a detailed molecular analysis of the tumor could not be performed. MGMT status was only available in 15 cases, with 8 cases/15 of MGMT promoter methylation (5 in the B arm, and 3 in the S arm).

### **Conclusion**

In summary, taken together, our results indicate that resection is safe and, compared to biopsy, is associated with a less severe deterioration of QOL and autonomy and, a significant although modest improvement of PFS in elderly patients suffering from newly diagnosed malignant glioma. Although resection did not provide a significant survival benefit, we believe that the risk/benefit analysis favors an attempt at optimal tumor resection in this population, providing careful preoperative geriatric evaluation. To select patients who will best benefit from the procedure, further trials are needed to better decipher the neurologic and systemic preoperative prognostic factors, particularly frailty<sup>25,26,27,28</sup>, and to objectively evaluate the weight of the extent of resection.

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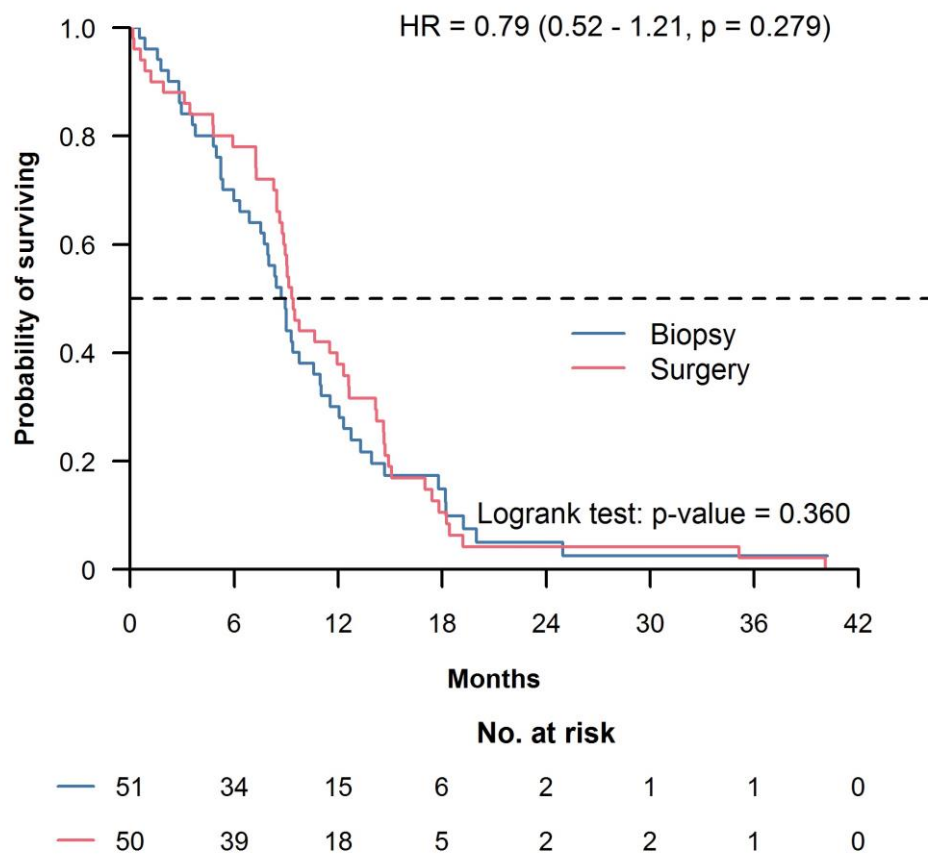
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**Figure legends:**

**Figure 1:** Overall survival Kaplan–Meier curves. No significant difference was found between the two groups (p value = 0.36). HR = adjusted HR for age, sex and Karnofsky performance score, with its CI 95% and associated p value



**Figure 2:** Kaplan–Meier curves of progression-free survival. A significant difference was found between the two groups, which was confirmed by multivariate analysis (p value = 0.012). HR = adjusted HR for age, sex and Karnofsky performance score, with its CI 95% and associated p value

