SAHLGRENSKA ACADEMY

Diffuse low-grade glioma and anaplastic glioma in the elderly

Degree Project in Medicine

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Gothenburg, Sweden 2019

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2. Abbreviations

LGG - Low grade glioma
2016 CNS WHO - 2016 World Health Organization Classification of Tumours in the Central Nervous System
PCV - Procarbazine-lomustine (CCNU)-vincristine
KPS - Karnofsky Performance Status
CRF - Case Report Form
RANO - Response Assessment in Neuro Oncology
FLAIR - Fluid-attenuated inversion recovery
fMRI - functional magnetic resonance imaging
nTMS - Navigated transcranial magnet stimulation
DTI - diffusion tensor imaging
IDH – Isocitrate dehydrogenase
FISH – Fluorescence in situ hybridization

3. Abstract

Introduction: Lower-grade glioma (WHO grade II and III) are malignant brain tumours that grow infiltratively and eventually transform into glioblastoma (grade IV) resulting in death. A negative prognostic marker following lower-grade glioma diagnosis is old age, but its covariance with other known prognostic factors and tumour biology remains elusive. In addition, impaired outcome following glioma diagnosis in the elderly may also be due to "ageism", where older patients receive suboptimal care.

Objective: Study differences in tumour characteristics, symptomatology, patterns of care and outcome in older and younger patients with lower-grade glioma.

Methods: We studied 69 patients (>50 years, older cohort) and 90 patients (18-50 years, younger cohort) with histopathological diagnosis of lower-grade glioma between 2010-2016 at Sahlgrenska University Hospital.

Results: Older patients presented more often with cognitive deficits (21.7% vs 6.7 %, p= 0.005) and focal deficits (37.7% vs 22.2%, p=0.033). They were more often biopsied and less often underwent resection compared to young patients (37.7% vs 14.4%, p=0.001) and their disease-specific survival were significantly impaired (p<0.001). Our preliminary findings suggests differences in the patterns of underlying mutations between the groups, with more IDH-wildtype lower-grade gliomas in the older group (p=0.011).

Conclusion: The impaired survival in elderly patients were probable due to a combination of negative prognostic factors, but where tumour biology presumably were of major importance.

4. Introduction

4.1 Classification

Glioma is a wide term for all types of tumours arising from glial cells, the non-neural supportive cells of the nervous system. *Diffuse infiltrative gliomas* are malignant tumours that share histological and genetic traits, more specifically they encompass the subtypes *astrocytoma and oligodendroglioma.* These tumours are histologically graded based on their degree of malignancy from II-IV. Grade II represents a low-grade glioma (LGG), grade III an intermediate anaplastic tumor and grade IV represents the most malignant tumour, also called glioblastoma. The new 2016 World Health Organization Classification of Tumours in the Central Nervous System (2016 CNS WHO) has now for the first time also introduced molecular markers to the classification system that further subdivides the tumours into three new groups based on their IDH-status (isocitrate dehydrogenase-status). These three new groups are IDH-mutation with 1p19q-codeletion in both chromosomes (canonical oligodendroglioma), IDH-mutation with intact 1p19q chromosomes (IDH-mutated astrocytoma) and IDH-wildtype (absence of any IDH-mutation) (1). *Figure 1* below presents a flowchart of the new glioma classification.

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes involved in the catalyzation of isocitrate. The role of IDH1 and IDH2 genes in glioma oncogenesis remains elusive but mutations in these genes often coexist with other genetic alterations such as 1p19q codeletions, TP53-mutations and ATRX loss. Recent research seem to indicate different pathophysiological processes for the development of IDH-mutated glioma and IDH-wildtype glioma (2).

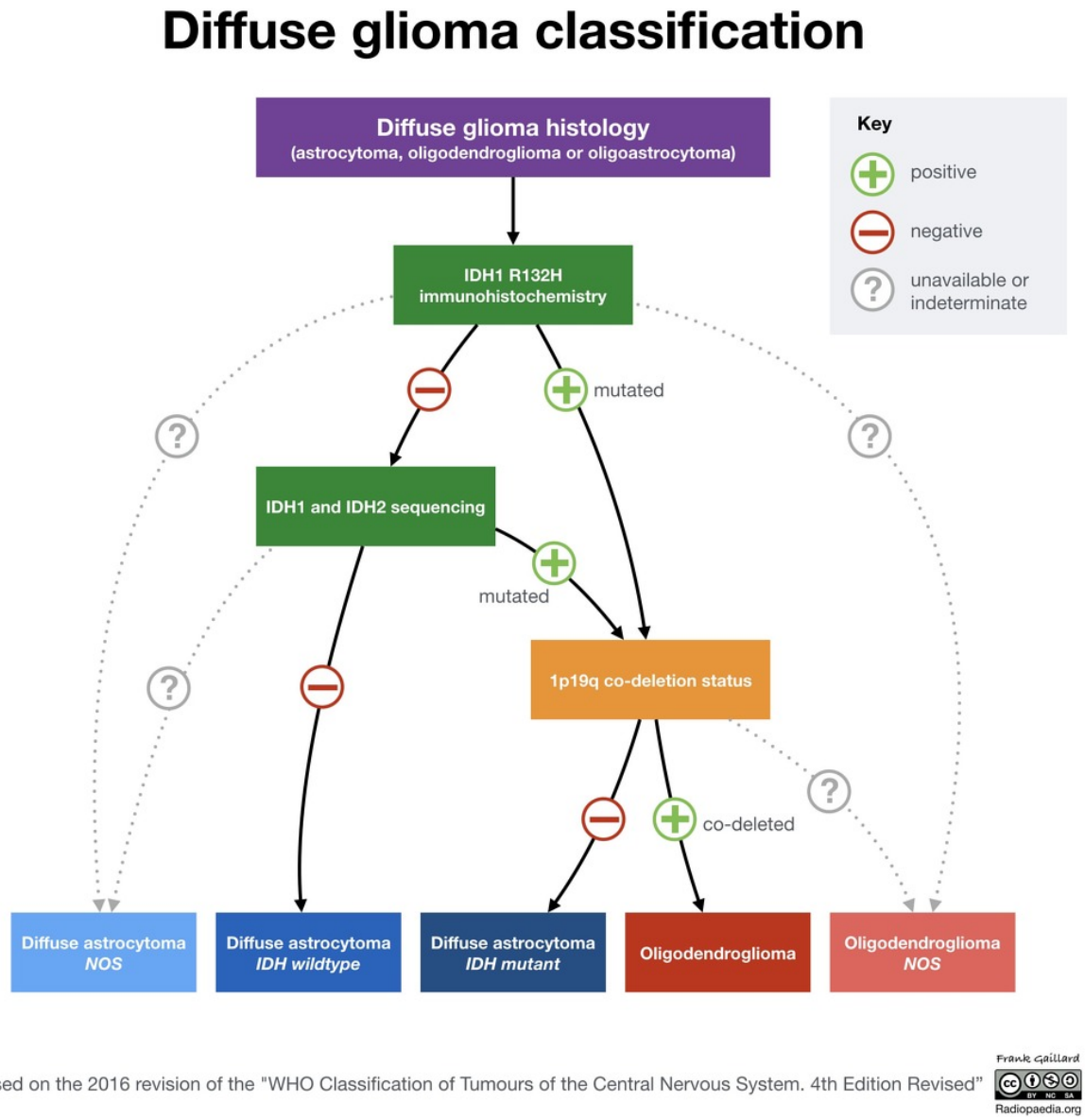

Figure 1. *Classification of diffuse glioma according to 2016 CNS WHO. Three separate tumours can be identified, Diffuse astrocytoma IDH-wildtype (absence of any IDH-mutation), Diffuse astrocytoma IDH-mutant (IDH-mutation with intact 1p19q chromosomes) and Oligodendroglioma (IDH-mutation with 1p19q-codeletion).*
IDH-status are assessed using immunohistochemistry but a complete assessment may also require genetic sequencing. 1p19q co-deletion status are assessed using fluorescence in situ hybridization (FISH) if either of IDH1 or IDH2 are found to be mutated on the immunohistochemistry or genetic sequencing.

The new integrated grouping system based on both phenotypical and molecular traits also group tumours into prognostic relevant subgroups where also treatment may differ. The presence of molecular markers such as IDH-mutation with 1p19q-codeletion and IDH-mutation with intact 1p19q chromosomes (i.e. IDH mutated astrocytoma) have in previous studies been linked to a more favorable prognosis (1). On the other hand the absence of an IDH-mutation, referred to as IDH-wildtype astrocytoma, has been linked to a negative outcome (1, 3). Following the introduction of molecular markers, the new term "lower-grade glioma" were introduced to encompass grade II and III tumours with distinct molecular patterns of IDH and 1p19q-status (3, 4). This complete redrawing of how tumours are classified have lead to the clear separation of oligodendroglioma and astrocytoma based on the occurrence or absence of IDH-mutations and 1p19-codeletion, and this has also lead to the disappearance of oligoastrocytomas, previously a common sub-entity in the 2007 WHO classification system (1, 5).

The natural history of lower-grade glioma is the inevitably transformation into a more malignant glioblastoma, referred to as a secondary glioblastoma. This tumour is usually different than the *primary* glioblastoma that develops de novo and is associated with elderly people and a shorter median overall survival. (1) However, survival after transformation to a secondary glioblastoma is as poor as for primary glioblastomas (6, 7). With the introduction of molecular markers it is apparent that most secondary gliomas are IDH mutated, while primary glioblastomas are IDH wild-type (8).

4.2 Epidemiology

Glioma is the most common type of malignant primary brain tumour (9), and range approximately as 10th most common cancer in Sweden (10). On the other hand, malignant gliomas take more life years than any other cancer at the individual level (11). Data from the Swedish Cancer Registry show that the average incidence rate of LGG in Sweden is

approximately 1/100,000 and for higher grade glioma about 5/100,000 (10). LGG often affect young adults with an incidence peak at age 30-44, although it is important to remember that LGG is also present in the elderly at fairly equal numbers. Anaplastic and glioblastoma tumours are more common in the elderly compared to the young and peak around an age of 65-79 (9, 10).

4.3 Clinical manifestations

In LGG, the most common presenting symptom at diagnosis is an epileptic seizure. Focal and cognitive deficits are more common in high-grade glioma (12). It is less common with headache as a presenting symptom, and headache rarely presents as the sole symptom, instead it is accompanied by other neurological deficits (13). An increased use of radiological imaging has also lead to a rising number of cases diagnosed as incidentalomas. Common reasons for finding a glioma incidentally are trauma and headache not related to tumor mass effect (14)

4.4 Diagnosis and additional testing

For lower-grade gliomas MRI is the radiological gold standard (15). The diffuse gliomas has a highly infiltrative growth within the brain and has a diffuse border in relation to the normal brain matter. Different MRI relaxation techniques (T1, T2) alongside Fluid-attenuated inversion recovery (FLAIR) are utilized to identify the dimensions of the tumor bulk. Contrast-enhancement (gadolinium-based) can be used to differentiate low-grade and high-grade glioma, where presence of enhancement normally indicative of a more vascularized and malignant tumour, but oligodendrogliomas quite frequently harbor non-specific mild contrast enhancement (16). On the other hand, almost a third of non-enhancing lesions typical for the low-grade glioma WHO grade II are in fact high-grade gliomas (17).

Low-grade glioma typically exhibits a hyperintense signal on the T2/FLAIR-image without

contrast enhancement on the T1-image. A typical glioblastoma presents with an irregular contrast enhancement, usually alongside its borders in a ring-formed manner. Glioblastoma also tends to exhibit a surrounding edema and a necrotic or hemorrhaging core. Glioblastoma may also be multifocal, displaying contrast enhancement in different areas of the brain. Low-grade glioma tumours undergoing malignant transformation usually exhibit radiographic transformation features on MRI prior to manifestation of worsening of symptoms (18).
A case description of typical radiological features are presented below in *figure 2.*
Many glioma patients are extensively investigated pre- and postoperatively with regard to differential diagnosis and brain function. Additional testing procedures can include; functional magnetic resonance imaging (fMRI) and navigated transcranial magnet stimulation (nTMS) for mapping the motor cortex and language center (lateralization), tractography for visualization of nerve tracts using diffusion tensor imaging (DTI) (19) and neuropsychological evaluation for assessing cognitive functions.

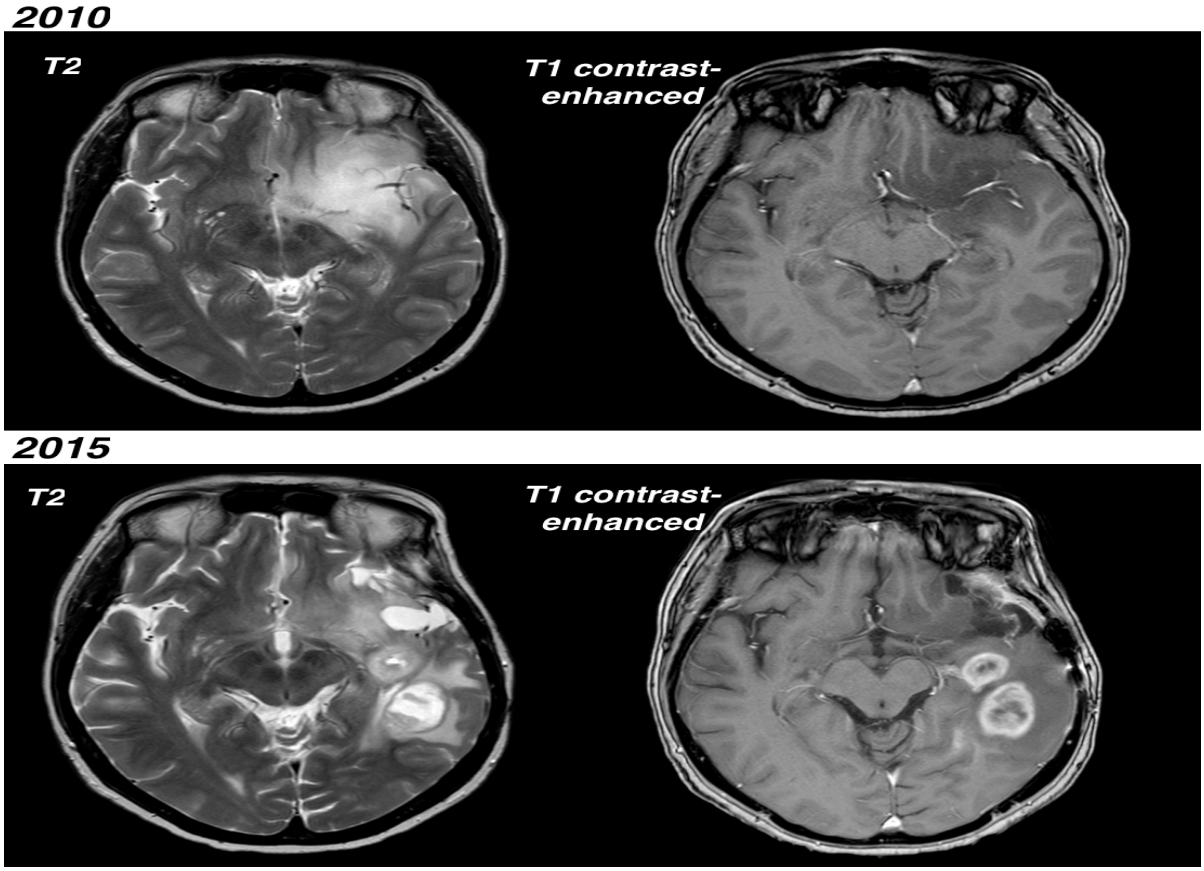

Figure 2. *Case description: 2010) Fifty year old female patient presenting with seizures. T2-weighted MRI shows a high signaling tumour with a moderately diffuse growth pattern in the left temporal and frontal lobe. T1-image with contrast did not exhibit any enhancement. Finding indicative of a low-grade glioma, histopathological diagnosis following resection was later confirmed to be a grade II astrocytoma. 2015) Same patient five years later, T1 contrast-enhanced image shows multifocal ring-formed contrast-enhancement in the left temporal lobe. Finding indicative of a malignant transformation to a glioblastoma.*

4.5 Neurosurgical and adjuvant treatment

Treatment consists of surgical resection of as much tumour tissue as possible without causing permanent and disabling injury. In low-grade glioma, a strategy favoring early radical resection compared to watchful waiting was associated with a clear survival advantage in a study from 2012 (20). Depending on tumour location and extension, biopsy is however the only reasonable option for some patients. Following histopathological diagnosis, radiation

therapy and/or chemotherapy with temozolomide or PCV (Procarbazine-lomustine-vincristine) can be of value in high-risk patients. A number of clinical trials on the subject of adjuvant treatment in grade II and grade III glioma have been conducted and treatment today is determined in a complex manner by carefully weighing together tumour characteristics, radiological features, performance status, disease progression and patient characteristics (21-25).

4.6 Prognostic factors

Established prognostic factors for glioma are tumour type, tumor size, age and Karnofsky performance status (KPS) (9, 26). KPS is a functional rating scale that measures symptom burden and how much the disease impacts normal activities in everyday life. The ten-degree scale ranges from 100% (no signs of disease or symptoms) to 0% (dead). A complete definition of KPS scoring criteria are presented in the appendices section's first page.
The overall 5-year relative survival varies significantly with tumour histology, grade II oligodendroglioma has a 5-year survival rate at 74.1% while anaplastic astrocytoma has a 5-year survival rate of just 10.8% (27). Prognosis based on molecular status show that IDH-wildtype carry the highest risk while IDH-mutations without 1p19q codeletion have an intermediate risk and IDH-mutations with 1p19q codeletion carry the lowest risk (3, 4). Old age has been shown to relate to a poor prognosis in glioma patients, but few studies have been devoted to this topic (9, 26, 28). A 2008 paper by *Chang et al* studying prognostic factors in hemispheric low-grade glioma found an age cut-off at patient age > 50 years as a negative prognostic factor (29).

4.7 Medical significance

Survival following glioma seems dependent on age (9, 26, 28). A recently published register based study from Sweden demonstrated that elderly patients with LGG are more often only

biopsied, and when resected they receive more complications and they survive shorter. One possible explanation could be that the tumours are radically different between the old and young, another possibility might be that the allocation of resources are different between the groups, i.e “ageism” (30).

Brain tumours are one of few tumours that are common among young people and low-grade glioma typically present in younger adults. This study will seek to highlight further knowledge about the presentation, underlying biology and treatment related factors with special focus on the elderly LGG patients.

4. Aim and Research questions

This study seeks to evaluate how tumour biology, symptomatology, patterns of care and clinical results differ in two patient groups; elderly and younger patients with “lower-grade glioma” that have undergone a neurosurgical procedure. Our hypothesis was that older people present with different tumour characteristics and perhaps as a consequence of this are treated differently than younger (e.g. more biopsies). Further, we hypothesize that older age is a negative prognostic factor. We intend to shed light on whether a negative outcome is due to widely different tumours or less aggressive therapy for comparable tumours.

4.1 Specific research questions

1. How do tumour biology differ in the two age groups?
2. What preoperative symptoms did younger and elderly patients present with?
3. What treatment and additional testing procedures were offered to the two groups?
4. How do the presence of surgical complications differ in the two groups?
5. Is the overall survival rate lower for elderly people?

5. Materials and Methods

5.1 Study design

This retrospective observational study includes patients at Sahlgrenska University hospital who underwent a biopsy or a neurosurgical resection for lower-grade glioma between 2010-2016. A list of patients undergoing surgery for lower-grade glioma were identified from the neurosurgical records and later supplemented with information about histopathology from the pathology department at Sahlgrenska University hospital. Inclusion criteria were a grade II and grade III glioma that were either an astrocytoma, oligodendroglioma or an oligoastrocytoma according to the WHO 2007 classification system. Exclusion criteria were patients < 18 years of age, all glioma of infratentorial origin and grade II and III glioma with a typical MRI finding of a glioblastoma (i.e sampling bias).

5.2 Study Population

192 patients were initially identified and 159 met the final inclusion criteria. A flow-chart of excluded patients is presented in the appendices section.

Mean age at diagnosis was 47.5 years. Males represented 58.5% of all glioma patients. The two subgroups analyzed were: older patients with age >50 (N= 69) and younger patients aged 18-50 (N= 90).

5.3 Data collection

Clinical, pathological and radiological data was collected from the patients medical records using a standardized Case-Report-Form (CRF). Information was collected about age, sex, tumour characteristics, preoperative symptoms, functional rating scale at time of diagnosis (Karnofsky Performance status), medical testing procedures, type of surgery, number of surgeries, adjuvant treatment, complications and radiological progression. See appendix for the CRF.

Information about preoperative tumor volume was measured using the open source software 3D slicer.

Information about tumour markers were collected from the medical records to the extent that they were available. 28 tissue sample specimens were also retested for molecular markers at the Sahlgrenska Cancer Center and our intention is to get the whole dataset classified for molecular markers in the near future. Data concerning death was obtained from the Swedish national death registry. The end of follow-up in this study was set to January 1st 2017.

5.4 Definitions

Primary surgery was defined as neurosurgical resection or biopsy following tumour diagnosis on MRI. As done by others, patients undergoing biopsy followed by resection less than 3 months later were classified as having a resection as their primary surgery (20). *First repeated surgery* was defined as the next neurosurgical resection following the primary surgery. Of the patients undergoing a repeated surgery, 24 patients did so due to progression in their disease (tumour recurrence), but five patients underwent reoperation prior to progression due to residual tumour mass on the postoperative MRI.

A definitive glioma diagnosis can only be obtained after histopathological examination following biopsy or surgery. If a patient who had already been given a histopathological

diagnosis later underwent a new biopsy or surgery less than 3 months afterwards and then received a different histopathological diagnosis (e.g. now grade III instead of II), than this second diagnosis would be considered the real primary diagnosis and the first diagnosis was considered due to a sampling error (e.g. caused by biopsy on the edge of the tumour). A patient who underwent a new biopsy or surgery more than three months afterwards and received for instance a diagnosis of a higher-grade gliomas was considered to have undergone a malignant transformation.

Clinical progression following surgery was assessed using the RANO-criteria (Response Assessment in Neuro-Oncology) (31). The first criteria was patients who developed new lesions or had an increase of their contrast enhancement on their follow-up MRI, these patients were considered to have undergone a radiological malignant transformation. The second criterion was patients who had a 25% increase of non-enhancing lesions on their MRI. The third criterion was a clinical deterioration that could only be explained by the tumour. Progression/transformation was assessed radiologically by continuously comparing the follow-up MRI with baseline-MRI after resection or best-response MRI following treatment. The changes on the MRI or the clinical deterioration were not to be attributable to “pseudo transformation” (effects from radiation or chemotherapy) or a significant change in corticosteroid usage.

General complications were assessed using the classification system introduced by Landriel Ibanez et al (32). In this paper, the authors define complications as “deviation from normal postoperative outcome within 30 days” and complications are then graded (I-IV) based on the severity of the condition and therapy used for treating complications. In addition, new neurological deficits following surgery were registered.

5.5 Statistics

SPSS, version 25.0 (Chicago, IL, USA) was used for statistical analyzes. Alpha-level of 0.05 was used for assessing statistically significant differences. Pearson's chi-squared test was used for testing association between categorical variables. Mann-Whitney U-test were used for assessing association between groups when the outcome variable was continuous, but not normally distributed. Kaplan-Meier plot analysis was used for comparing survival between the two groups and curves were compared using the log-rank test. Cox-regression models were used for comparing how different possible predictors affected survival.

6. Ethics

Patient data was kept de-identified at a safe location within Sahlgrenska University Hospital. Approval from the Regional ethics board was obtained prior to study initiation.

7. Results

7.1 Demographics and tumour characteristics

Within the younger group, 90 patients (56.6%) were identified and the mean age at diagnosis was 36.7 years (SD 8.6 years). The older group included 69 patients (43.4%) and the mean age at diagnosis was 61.6 years (SD 6.6 years). Males were slightly overrepresented in both groups (62.3% in old and 58.4% in young group).

The total number of grade II (N=81) and grade III (N=78) tumours were distributed somewhat surprisingly, with grade II tumours being proportionally more frequent within the old group (p=0.028). There were no significant differences in tumour histology (table 1).

We were able to retrieve molecular markers in 70 patients, thus in 89 patients we could not evaluate molecular markers. IDH-wildtype was more common in the old group (N=10, 34.5% vs N=4, 9.8%, p=0.011). Preoperative tumour volume was found to vary greatly between individual patients. However, there was no significant difference in preoperative median tumour volume between the two age groups, young patients had a median tumour volume of 70.3 cm^3 compared to 88.8 cm^3 in old patients (p=0.130). A full description of demographic features and tumour characteristics are presented in Table 1.

Table 1. *Demographics and tumour characteristics after primary surgery*

	18-50 N=90 (56.6%)	**>50** N=69 (43.3%)	**P-value**
Male sex, N (%)	50 (58.4)	43 (62.3)	
Mean age at diagnosis (SD)	36.7 (8.6)	61.6 (6.6)	
Grade II, N=81	39 (43.3)	42 (60.9)	
Grade III, N=78	51 (56.7)	27 (39.1)	**0.028**
Astrocytoma Grade II, N (%)	25 (27.8)	28 (40.6)	0.09
Astrocytoma Grade III, N (%)	29 (32.2)	16 (23.2)	0.210
Oligoastrocytoma II, N (%)	9 (10.0)	7 (10.1)	0.976
Oligoastrocytoma III, N (%)	16 (17.8)	6 (8.7)	0.100
Oligodendroglioma II, N (%)	5 (5.6)	7 (10.1)	0.278
Oligodendroglioma III, N (%)	6 (6.7)	5 (7.2)	0.886
Molecular markers N, (%)			
IDH-wildtype (high risk)	4/41 (9.8)	10/29 (34.5)	**0.011**
IDH-mutation - Non 1p19q-codeletion (intermediate risk)	11/41 (26.8)	6/29 (20.7)	0.490
IDH -mutation – 1p19q-codeletion (low risk)	23/41 (56.1)	12/29 (41.4)	0.155
IDH-mutation (not tested for 1p19q-codeletion)	3/41 (7.3)	1/29 (3.4)	N/A
Tumor markers not assessed	49	40	
Tumour size			
Median tumour size in cm^3 (Range)	52.5 *cm^3* (3.1 – 373.4 *cm^3*)	67.0 *cm^3* (2.4 – 464.2 *cm^3*)	0.130
Missing, (N=16)	(7)	(9)	

% represents percentage *within* each group, e.g. there were 25 patients with grade II astrocytomas within the young group(N=90) representing 27.8 % of all tumours in the young.

7.2 Presenting symptoms

Seizure was the most common presenting symptom in both the younger (72.2%) and the older (63.8%). Seizure as the sole presenting symptom was significantly more frequent in the young group with 55.6% of patients presenting with no other symptoms than seizure compared to 34.8% in the old group (p=0.009). Headache as a presenting symptom was also significantly more common in the young group (p=0.008). Headache usually presented alongside other symptoms and headache as the only presenting symptom was very rare in both groups (N=7). The presence of cognitive changes at diagnosis was significantly more common in the old group compared to the young (p=0.005). Focal deficit symptoms were also significantly more frequent in the old group (p=0.033). No difference was observed in the symptom duration or performance status at time of diagnosis. Detailed description of presenting symptoms is presented in Table 2.

Table 2. *Presenting symptoms*

	18-50 (N=90)	**≥50** (N=69)	**P-value**
Asymptomatic/Incidentaloma, N (%)	6 (6.7)	7 (10.1)	0.43
Seizure, N (%)	65 (72.2)	44 (63.8)	0.26
Seizure only, N (%)	50 (55.6)	24 (34.8)	**0.009**
Headache, N (%)	28 (31.1)	9 (13.0)	**0.008**
Cognitive changes, N (%)	6 (6.7)	15 (21.7)	**0.005**
Focal deficit symptoms, N (%)	20 (22.2)	26 (37.7)	**0.033**
Motor deficit	11 (12.2)	14 (20.3)	0.17
Language deficit	6 (6.7)	8 (11.6)	0.28
Visual deficit	3 (3.3)	4 (5.8)	N/A
Other symptoms*, N (%)	7 (7.8)	11 (15.9)	0.11
Symptom duration, N (%)			0.69
< 30 week	67 (74.4)	48 (70.0)	
> 30 weeks	17 (18.9)	14 (20.3)	
(Missing/Asymptomatic, N=13)			

Karnofsky performance status, N (%)			0.84
100	21 (23.3)	19 (27.0)	
90	30 (33.3)	21 (30.4)	
80	22 (24.4)	14 (20.2)	
70 or less	17 (18.9)	15 (21.7)	

*Other symptoms included sensory disturbances(N=10), dizziness(N=9), Syncope(N=1), Dysphagia(N=1).

7.3 Treatment and additional testing

Old patients more often underwent biopsy only procedures (37.7%) instead of resection compared to the young group (14.4%), with a statistically significant difference (p=0.001). Mapping procedures (awake mapping or motor mapping asleep) during resection were less often offered to the older group (p= 0.025). Only one (2.3%) patient in the old group underwent an awake mapping procedure compared to 12 patients (15.6%) in the young group. Mean age for patients undergoing awake mapping procedures were 36.8 years. There was no other significant difference with regard to intraoperative tools used during resection between the age groups. The old group also seemed to be offered less additional testing procedures but there was only a significant difference between the groups in regard to neuropsychology assessments pre-/postoperatively. Table 3 presents an overview of the neurosurgical treatment and testing procedures offered to the two groups.

Table 3. *Primary neurosurgical treatment and additional testing procedures*

	18-50 (N= 90)	**>50** (N=69)	**P-value**
Biopsy only, N (%)	13 (14.4)	26 (37.7)	**0.001**
Resection*, N (%)	77 (85.6)	43 (62.3)	
Tools used intraoperatively, N (%)			
Ultrasound	39 (50.6)	21 (48.8)	0.849
Neuronavigation	55 (71.4)	26 (60.5)	0.219

5-ALA	5 (9.1)	2 (4.7)	N/A
Mapping procedure	15 (19.5)	2 (4.7)	**0.025**
-Awake mapping	12 (15.6)	1 (2.3)	
-Motor mapping asleep	3 (3.9)	1 (2.3)	
Additional testing procedures, N (%)			
Navigated transcranial magnetic stimulation	14 (16.0)	7 (10.1)	0.318
Speech therapist assessment	5 (5.6)	5 (7.2)	N/A
Neuropsychology assessment	33 (36.7)	15 (21.7)	**0.042**
Other test (Tractography, fMRI)	12(13.3)	5 (7.2)	0.218

* indicates resection as the primary neurosurgical procedure or biopsy followed by resection within 3 months.

There were 46 older patients (66.6%) and 55 (61.1%) of younger patients who underwent treatment with chemotherapy (p=0.471). However when broken down in to treatment in respect to tumour grade in the groups, we could observe that chemotherapy were more frequently administered to old patients (57.1%) with grade II tumours than young patients (30.8%) with grade II tumours (p=0.017). No significant difference was observed between the two groups when comparing the administration of chemotherapy in grade III tumours. However treatment with PCV for grade III tumours was more common in the young group, especially PCV-treatment subsequent to radiotherapy.

In a similar manner we observed no difference between overall treatment with radiotherapy when looking at both grade II and III tumours. However elderly patients with grade II tumours received more radiotherapy compared to the young group (p=0.028) and young patients with grade III tumours received more radiotherapy compared to the old group (p=0.020). Regarding the modality of radiotherapy offered, no difference was observed in the administration of photon therapy and proton therapy between the two groups.

The mean absorbed radiation dose administered to the patients was higher in the young group

compared to the old (p=0.037). However, we identified five cases of outliers in the sample who represented patients who had either been forced to terminate radiotherapy prematurely (N=1) or had been given a modified low-dosage treatment (N=4) of less than 34 Gy due to disease related circumstances. Four out of these outliers were elderly patients and when they were removed from the analysis there was no significant difference in administered radiotherapy dose between the older (median 54.0 Gy, range 30.0-60.0) and the young (59.4 Gy, range 40.0-66.0). *Table 4* outlines an overview of adjuvant treatment.

Table 4. *Adjuvant treatment offered to the patients before any repeated surgery*

	18-50 (Grade II, N=39) (Grade III, N=51)	**>50** (Grade II, N=42) (Grade III, N=27)	**P-value**
Chemotherapy, N (%)	55 (61.1%)	46 (66.6%)	0.471
Chemotherapy, Grade II	12 (30.8)	24 (57.1)	**0.017**
Temozolomide	10	22	
*PCV**	2	2	
Chemotherapy, Grade III	43 (84.3)	22 (81.5)	0.749
Temozolomide	34	21	
*PCV**	9	1	
Radiation therapy, N (%)	56 (62.2)	39 (56.5)	0.560
Radiotherapy, Grade II	13 (33.3)	21 (50.0)	**0.028**
Radiotherapy Grade III	43 (84.3)	18 (66.7)	**0.020**
Radiation modality, N (%)*y*	51 (56.6)	36 (52.2)	0.573
Photon therapy	5 (5.6)	3 (4.3)	0.730
Proton therapy			
Accumulated Radiation dose, Median Gy (Range)	59.4 Gy (40.0-66.0)	54.0 Gy (30.0 -60.0)	**0.037**

*Procarbazine-lomustine (CCNU)-vincristine

7.4 Postoperative complications

Elderly patients suffered more general complications within 30 days following resection than the young, however we observed no significant difference between the two patient groups. There was an overweight of complications requiring intervention with general anaesthesia in the younger group, this was mainly due to six cases of postoperative intracranial infection requiring reoperation with partial removal of the skull in this group compared to one case in the old group. Of all the 34 general complications, 30 of them occurred after a resection and just three complications (two cases of venous thromboembolism and one case of refractory status epilepticus resulting in death within 1 day) were observed after biopsies. All general complications are listed below in *table 5.*

Regarding postoperative outcome (new focal neurological complication following resection), language and motor complications were the most frequent in both groups. Again, there was no difference between groups. There was no significant difference in the frequency of permanent neurological complications. *Table 5* provide a detailed overview of complications.

Table 5. *Postoperative complications (resections only)*

	18-50 (N=77)	**>50** (N=43)	**P-value**
General complications within 30 days following resection*, N (%)	17 (22.1)	10 (23.3)	0.882
Grade Ia, no drugs	1	4	N/A
Grade Ib, drugs	6	4	N/A
Grade IIa, intervention without general anesthesia	1	1	N/A
Grade IIb, intervention with general anesthesia	8	1	N/A
Grade IIIa, Single organ failure, Intensive care unit	1	0	N/A
Neurological outcome following resection, N (%)			
Motor complications	12 (15.6)	10 (23.3)	0.298
Permanent(>3 months)	6 (7.8)	4 (9.3)	
Language complications	16 (20.8)	11 (25.7)	0.546
Permanent(>3 months)	8 (10.4)	8 (18.6)	
Cognitive complications	5 (6.5)	6 (14.0)	N/A
Permanent(>3 months)	2 (2.6)	4 (9.3)	
Visual complications	5 (6.5)	6 (14.0)	N/A
Permanent(>3 months)	1 (1.3)	3 (7.0)	
Cranial nerve complications	1 (1.3)	0	N/A
Permanent(>3 months)	0	0	
Worsening of seizure	1 (1.3)	2 (4.6)	N/A
Postoperative rehabilitation following resection	13 (16.9)	6 (14.0)	0.673

* General complications were: postoperative intracranial infection requiring reoperation (N=7), Brain edema requiring new or adjusted dose corticosteroids (N=3), Subdural hematoma (N=2), Venous thromboembolism (N=2), Scalp abscess (N=2), Scalp infection (N=2), Intracerebral hematoma (N=2), Hemorrhagic infarction (N=1), Asystole (N=1), CSF-rhinorrhea requiring reoperation (N=1), Extracranial edema (N=1), Extracranial hematoma (N=1), Urinary tract infection (N=1), Caliciviridae infection (N=1), Postoperative fever of unknown origin (N=1), Surgically induced first-time epileptic seizure (N=1), Miscarriage during pregnancy (N=1).

7.5 Outcome

RANO-criteria (criteria 1 to 3) was used for assessing clinical progression. Significantly more patients in the older group were found to have progressed or undergone a malignant transformation compared to the younger group ($p<0.001$). In the older group, 66.7% of the patients met one of the RANO-criteria whereas only 36.7% did so in the younger group. In both groups, malignant transformation (criteria 1) on follow-up MRI was the most frequently met criteria. We found that 55 patients (69.6%) of patients who met any RANO-criteria had died compared to 30.4% who were still alive as of end of follow-up ($p<0.001$). Median survival was just eight months in the patients who met any RANO-criteria.

Despite that elderly patients progressed more frequently in their disease, only 10.1% of old patients were offered a repeated surgery compared to 24.4% in the young group ($p=0.021$). *Table 6* details the specifics about progression and repeated treatment.

Table 4. *Clinical progression and repeated treatment*

	18-50 (N=90)	**>50** (N=69)	**P-value**
Clinical progression (RANO-criteria, 1-3), N (%)	33 (36.6)	46 (66.7)	**<0.001**
1. Any new lesion or increase of contrast enhancement on MRI (malignant transformation)	23	30	**0.017**
2. T2 or FLAIR MRI with a 25% increase of non-enhancing lesion	7	7	0.602
3. Clinical deterioration	3	9	**0.022**
Repeated resection, N (%)	22 (24.4)	7 (10.1)	**0.021**
Chemotherapy following repeated surgery, N (%)	18 (81.8)	5 (71.4)	0,554
Radiation following repeated surgery, N (%)	14 (63.6)	4 (57.1)	0,757
Deceased due to tumor during follow-up, N (%)	20 (22.2)	36 (52.2)	**<0.001**

38 elderly patients had died at the end of follow-up compared to 21 patients in the young group. Three patients (two in the old group and one in the young group) died during the follow-up period from diseases unrelated to their glioma diagnosis and before reaching any of the RANO-criteria for progression. The cause of death in these instances were gastric cancer, aspiration pneumonia in a patient who was suspected of having developed a motor neuron disease and sepsis brought on by a limb infection. These patients were censored in the survival analysis, meaning that the disease-specific survival was 22.2 % in the young group and 52.2% in the old group during follow-up.

Disease-specific survival over time between the groups was assessed using a Kaplan-Meier analysis plot (log-rank $p<0.001$) and are presented in *figure 3.* Twenty months after surgery, 60% of patients in the older group were still alive versus 90% of patients in the younger group. Forty months following surgery only 38% of patients in the old group were still alive compared to 82% in the young group. The median decease related survival was 29 months in the older group (95 % CI 16.3-35.7) while median survival was not reached for the younger group. When comparing survival over time stratified and looking only on patients who underwent a resection, the difference between the two groups was smaller but still significant (log-rank $p<0.001$, *figure 4*).

Survival was dependent on the type of neurosurgical treatment. *Figure 5* outlines a comparison of survival between all patients who underwent resection versus patients who were only biopsied.

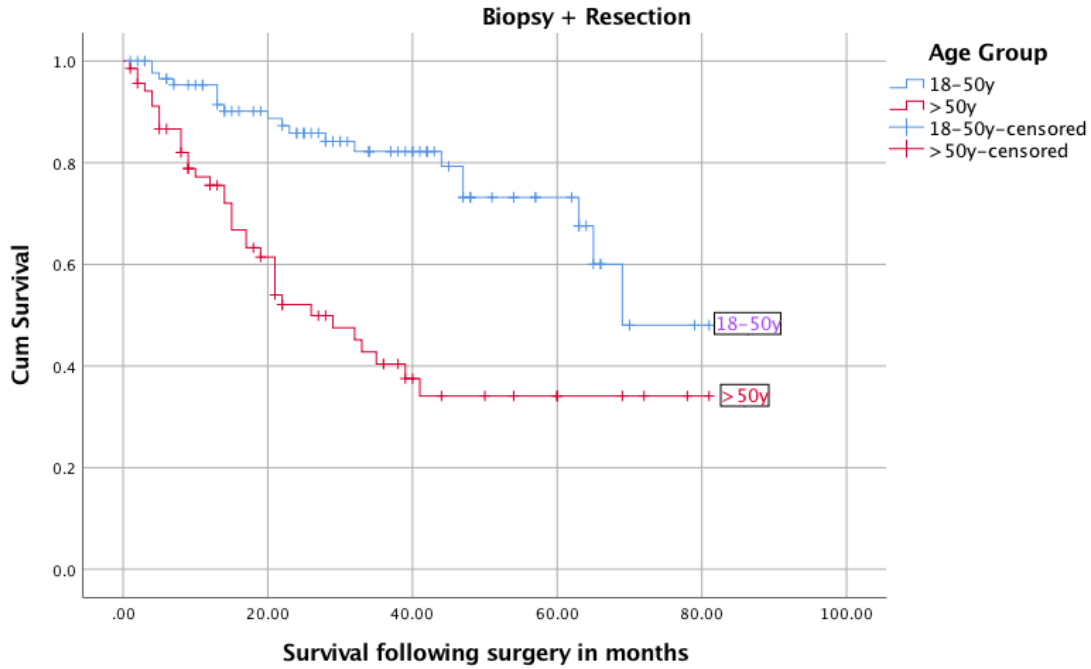

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Figure 3. *Survival following surgery in months between the two age groups. 18-50y (N=90), >50y (N=69). Log-rank p-value <0.001*

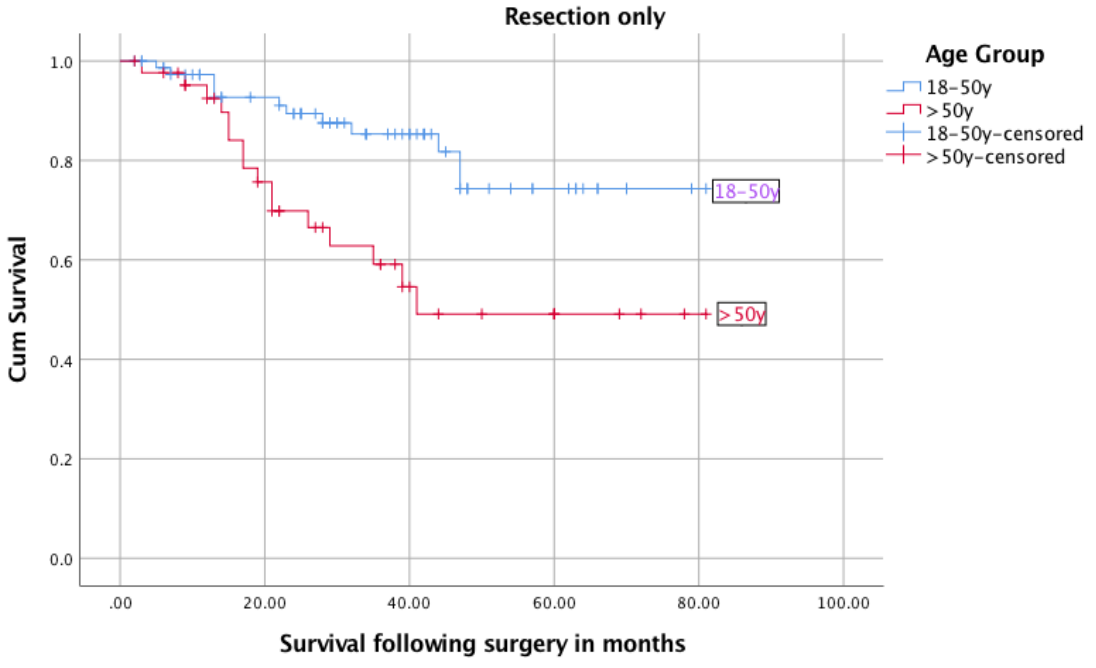

Figure 4. *Survival between age groups following surgery in patients who underwent resection. 18-50 (N=77), >50 (N=43). Log-rank p <0.001.*

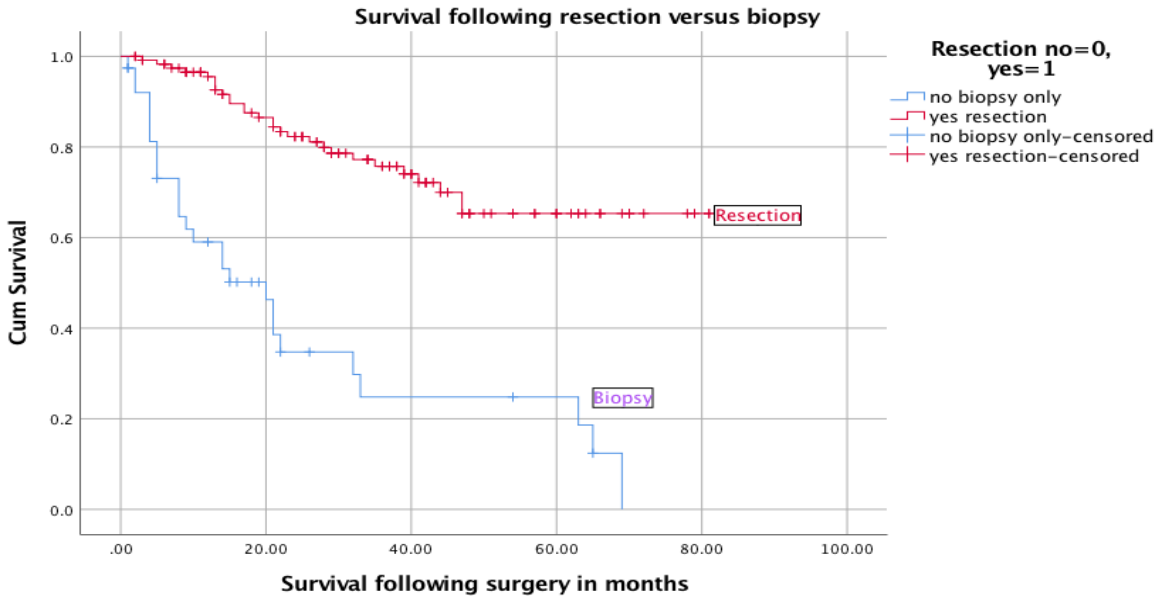

Figure 5. *Comparison of survival following resection(N=120) versus biopsy(N=39) in all patients. Log-rank p-value < 0.001.*

Survival varied with presenting symptoms. Patients who presented with only seizure had a survival advantage compared to patients who also presented with other symptoms (*figure 6*). In a similar manner, patients presenting with Karnofsky performance status of 100 or 90 had a better survival compared to patients who had a low Karnofsky performance status of 80 or less (*figure 7*).

We observed no difference in survival between grade II and grade III tumours when looking at all patients, log-rank p-value = 0.462 (*figure 8*). When classifying patients into 3 risk categories based on their IDH-status (high-risk IDH-wildtype, intermediate risk IDH-mutation non 1p19q-codeletion, low-risk IDH-mutation 1p19q codeletion) we observed a significant survival disadvantage in the IDH-wildtype group. Unfortunately, 89 patients did not have their tumour markers assessed yet and were missing in the analysis. See *Figure 9*.

We observed no significant difference in survival when comparing survival between age groups, looking only at patients with IDH-mutations. See *figure 10.*

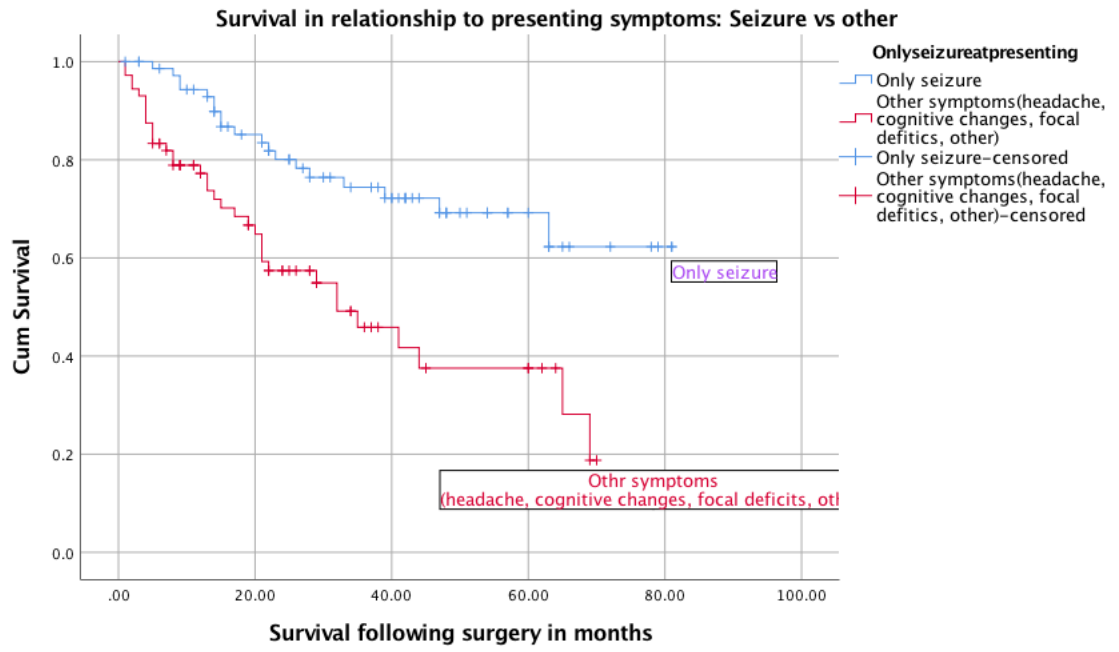

Figure 6. *Survival in relationship to presenting symptoms in all patients. Log-rank p-value < 0.001. Only seizure (N=74), Other symptoms (N=72). Missing=Incidentaloma (N=13).*

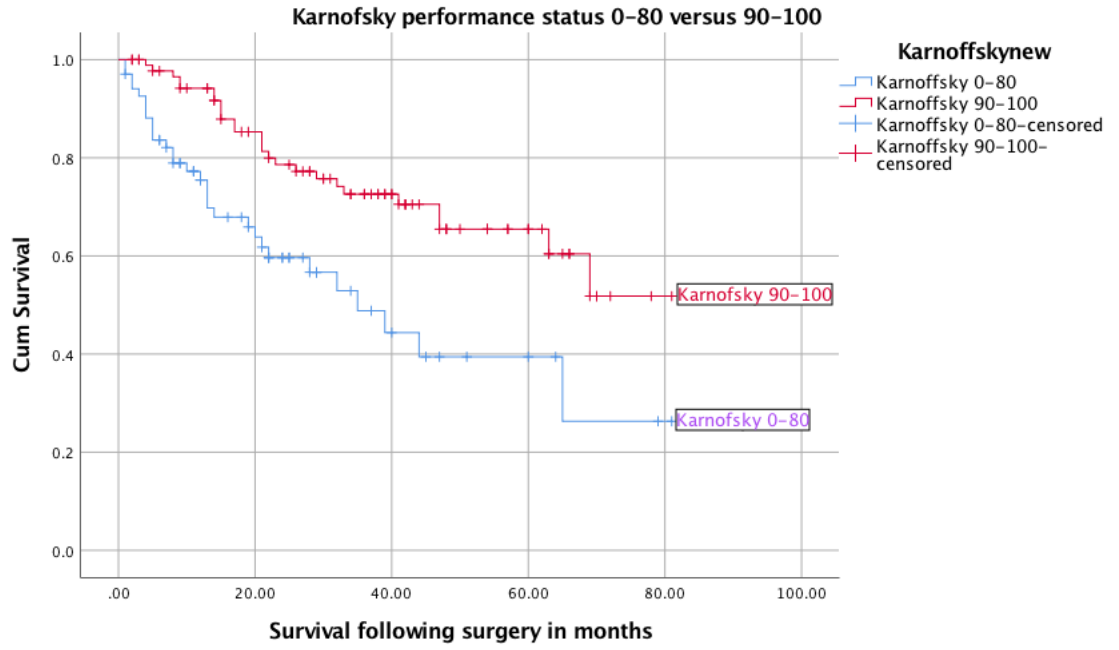

Figure 7. *Survival at different Karnofsky performance status in all patients. Log-rank p-value =.,001. Karnofsky 90-100 (N=91), Karnofsky 80 or less (N=68).*

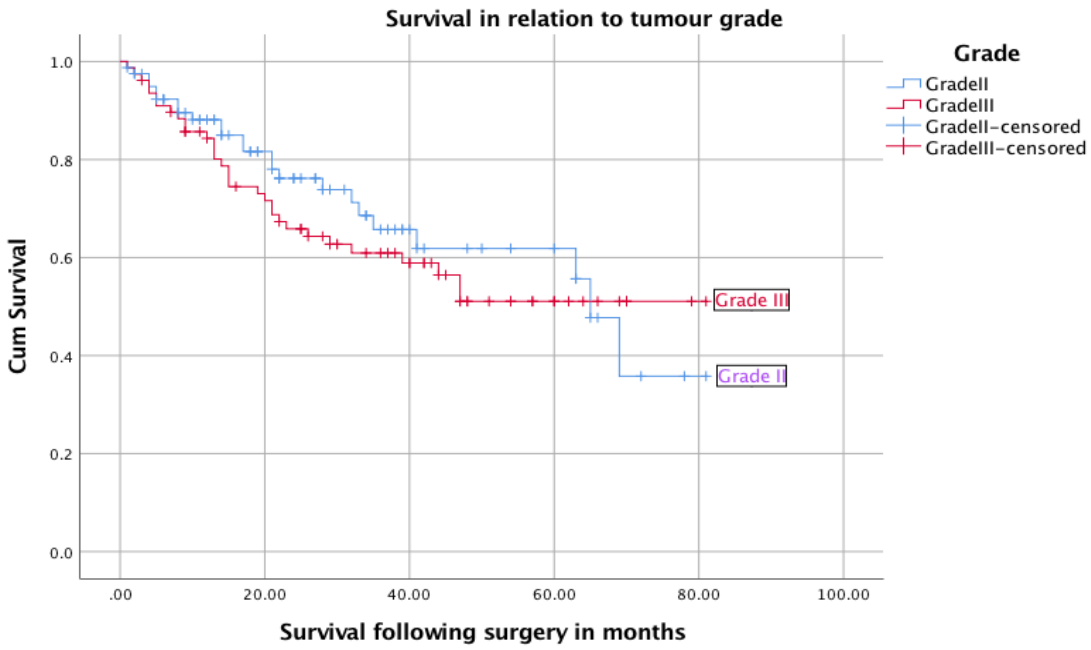

Figure 8. *Survival in grade II (N=81), grade III (N=78) tumours. Log-rank p-value =0.462.*

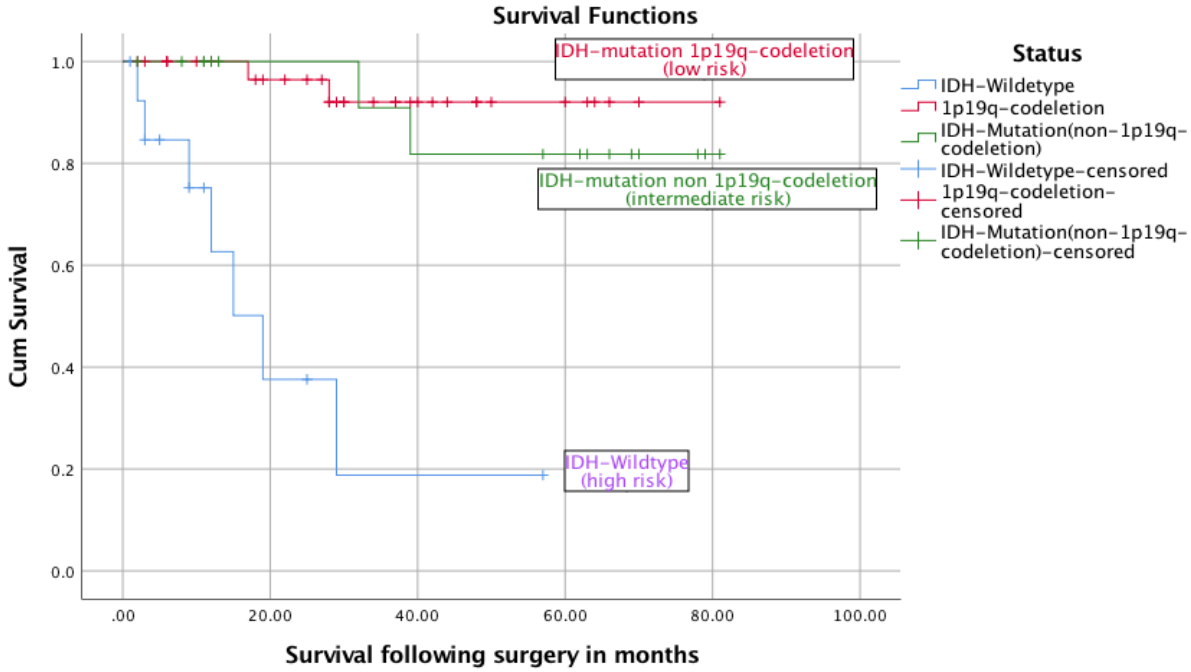

Figure 9. *Survival according to IDH-status. Log-rank p-value < 0,001.*
IDH-mutation 1p19q-codeletion (N=35)
IDH-mutation non 1p19q-codeletion (N=17).
IDH-wildtype (N=14).
Missing=93 (89 tumour markers not assessed, 4 IDH-mutations with unknown 1p19q-status).

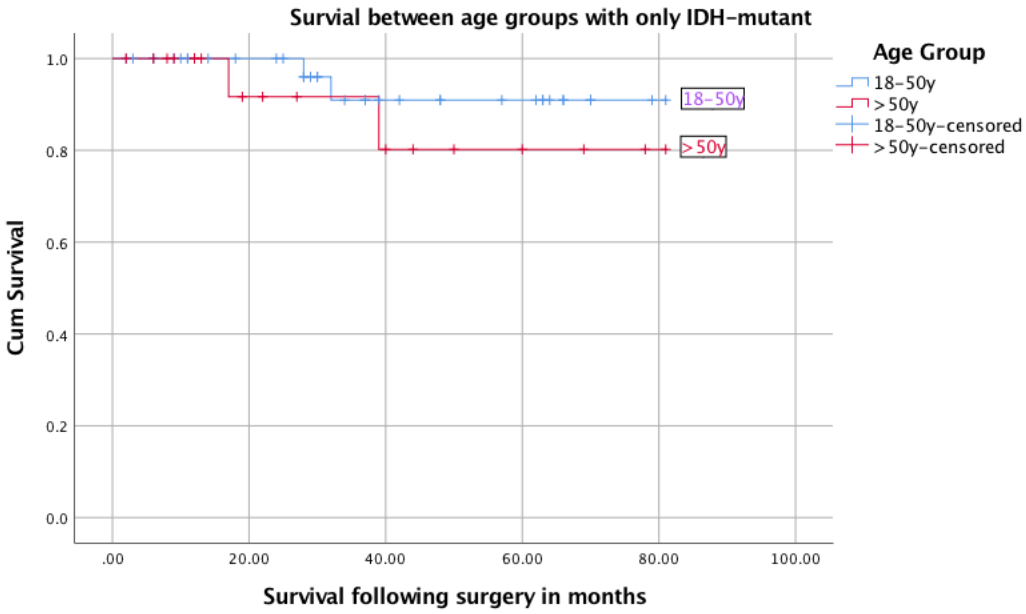

Figure 10. Survival according to IDH-mutant status, IDH-wildtype excluded. Log-rank p-value =0,372.
IDH-mutation 1p19q (N=35)
IDH-mutation non 1p19q (N=17)
IDH-mutation non 1p19q (N=4)

We used a Cox multivariable model to study survival in the different age groups when also including other underlying predictors. The first model was adjusted for sex, tumour grade (II or III), Karnofsky performance status (KPS 100-90 vs KPS <90) and preoperative tumour size in ml. KPS, grade and age were all significant predictors while sex and tumour size were not significant. Survival in the older group was significantly impaired compared to the younger group when adjusted for these underlying predictors ($p < 0.001$, see *figure 11*).

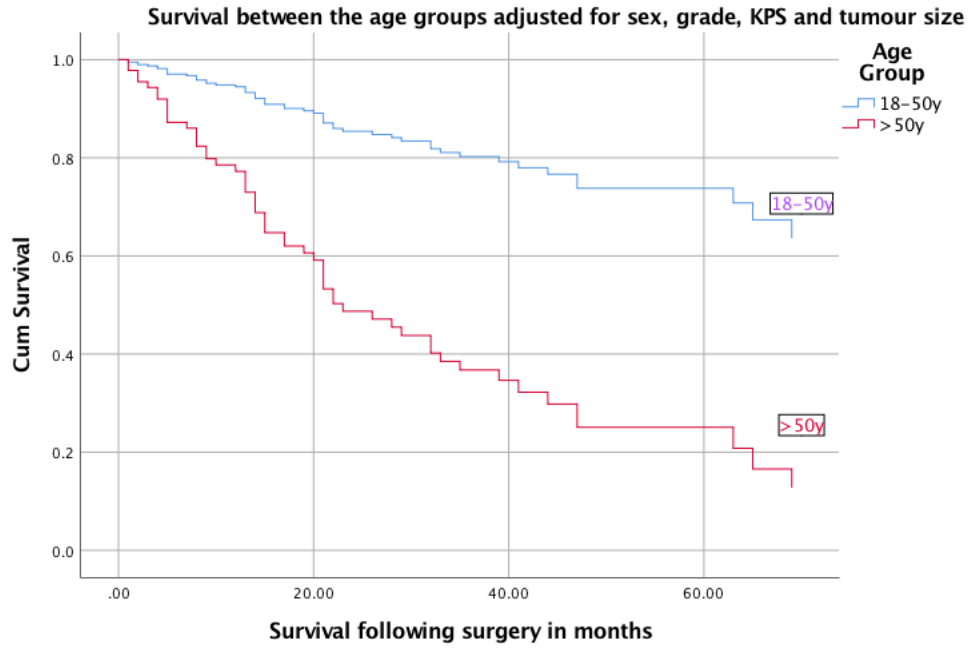

Figure 11. *Survival adjusted for sex, grade, KPS and tumour size. Missing = 16, did not have their tumour size measured.*

The second Cox-regression model analyzed survival between age groups adjusted for sex, tumour grade, KPS and IDH-status (high-risk IDH-wildtype or low-intermediate risk IDH-mutation) and is presented in *figure 12.* The model still demonstrated that older age had a survival disadvantage compared to the younger group. IDH-wildtype hazard ratio was 25.3 (95 % CI 4.3 -150.3) compared to having IDH-mutation.

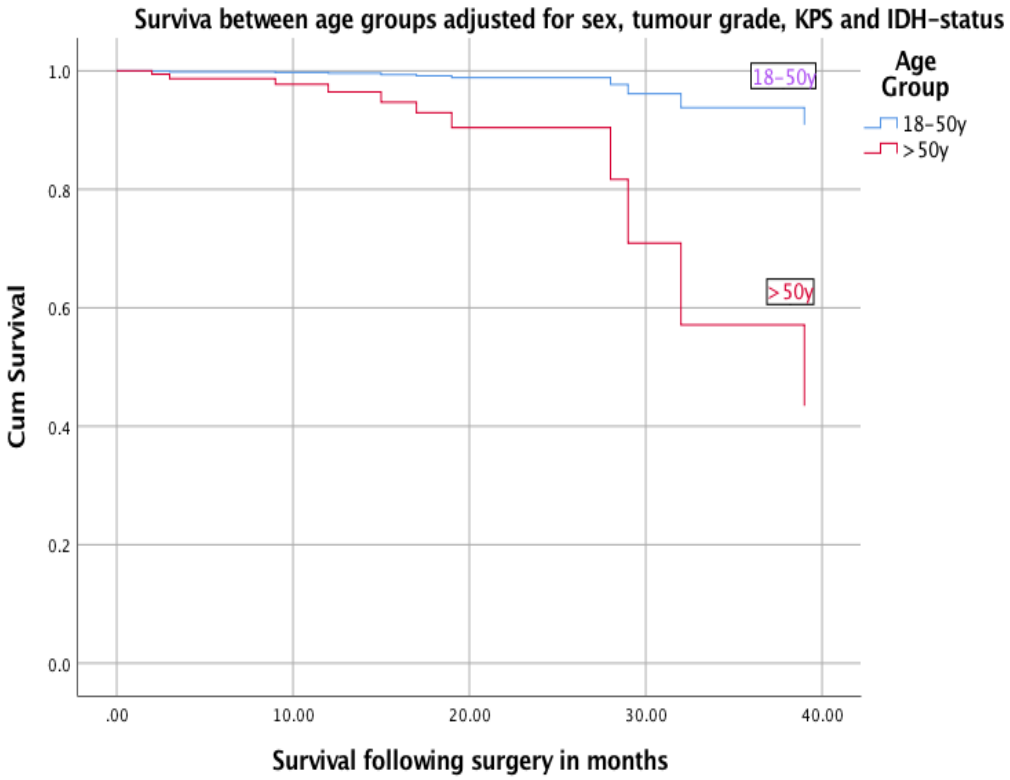

Figure 12. *Survival between age groups adjusted for sex, tumour grade, KPS and IDH-status.*
High-risk wildtype IDH (N=14).
Low-intermediate risk IDH-mutation (1p19q codeletion + non 1p19q codeletion) (N=56).
Missing = tumour markers not assessed (N=89).

8. Discussion

8.1 Main findings

This study compared tumour biology, presentation, patterns of care and outcome in lower-grade glioma patients in a younger (18-50) and older (>50) cohort. Neurological deficits were more frequent in older patients compared to younger patients. Disease-specific survival was significantly lower in the older group compared to the younger group. Elderly patients were more often only offered a biopsy procedure, nevertheless patients in the old group still had a significantly lower survival than young patients when comparing only for resections. Although preliminary, we documented that molecular markers were highly associated with age. Somewhat different treatment and tools were provided but we did not find strong evidence of "ageism". The observed differences in treatment related factors might be readily explained by differences in tumor characteristics and presentation, although intraoperative mapping was perhaps underused in the older group of patients.

8.2 Tumour characteristics

Interestingly, patients in the older cohort had more grade II tumours compared to the younger cohort and elderly patients should then seemingly have an advantage in tumour biology according to the 2007 WHO classification system (5). Still, we found that their survival was significantly impaired compared to the younger. Previous studies have observed the problem of interobserver variation in traditional diagnosis of lower-grade glioma (33, 34) and the clinical implementation of molecular markers can improve this inaccuracy in diagnosis as well as lending itself as a more accurate prognostic marker (4). However, in WHO 2016 grade is still used and molecular markers is for subgrouping within the group, although this may be revised due to the abovementioned problems. We did not have molecular data for all patients but our preliminary findings strongly suggests that IDH-wildtype is more common in the

older group of lower-grade glioma, something that is in accordance with previous literature (35, 36). “The Cancer Genome Atlas” (TCGA) which analyzed 293 patients with lower-grade glioma found that molecular markers based on IDH and 1p19q-status are superior to histology-based classification and that IDH-wildtype low-grade glioma are more similar to glioblastoma with a worse outcome (4). When IDH wildtype tumors were excluded from our analysis, the additional impact of age was in fact rather marginal.

8.3 Presenting symptoms

Seizure was the most frequently registered presenting symptom in both cohorts, younger patients more often presented with only seizures while older patients more often presented with cognitive changes and focal deficits. These findings are in accordance with previous research into the symptomatology of glioma (13, 29, 30)

Patients presenting with low symptom burden, that is high functional performance status at time of diagnosis, were associated with better survival than those who did not. However there was no significant difference in performance status between the old and young group. The findings on this are not in line with other works in the literature which link patient age with worse functional status (12, 30) but this may be due to a difference in sample with more grade II tumours in the older group than reported in other works (12, 15).

Treatment

Jakola et al demonstrated that early radical resection correlated with an improved survival over a strategy with watchful waiting and biopsy in the treatment of low-grade glioma (20, 37). Like previous studies, we found that older patients receive less aggressive therapy with less resections compared to biopsies (30, 38). However, this study also investigated pre- and intraoperative tools used for resection and found that old patients less often undergo resection with awake mapping or motor mapping asleep. The surgical use of “intraoperative stimulation mapping” (ISM) were assessed in a 2010 metanalysis by *De Witt Hamer et al* and found that

usage of ISM correlates with more extensive resection which in turn is associated with longer survival (39). Although this study currently lacks data on anatomical tumour location and eloquent tumour localization, our findings of 19.5 % of younger patients undergoing any mapping procedure compared to 4.7 % of older patients might suggests an unequal allocation of resources between young and old patients. *De Witt Hamer et al* argues for two scenarios where the use of ISM is unfavorable, the first being related to localization and the second involving patients who might not benefit from the reduced permanent deficits in compensation for increased transitory deficits (39). Old patients with a low functional status and an expected shorter survival may fit this second criterion, however this study did not identify any significant difference in functional performance status between the age groups.

Other studies have reported the importance of how maximum extent of resection (EOR) and minimum residual tumour volume impacts survival in low-grade glioma tough the exact dimensions of the EOR required for a meaningful survival advantage remains under debate (40-42). Unfortunately, this study did not yet have information about the postoperative extent of resection between the age groups. We can however show that patients in the old cohort were offered a repeated surgery less often than the young cohort, something that has been linked to impaired survival following recurrence in low-grade glioma (43), for high-grade glioma there is no consensus in the scientific community on the role of repeated surgery (44).

Adjuvant treatments were investigated as treatment-related factors that might influence outcome in the two patient groups. Overall we found no significant difference in the number of patients who received chemotherapy or radiation therapy when looking at both grade II and III tumours. The difference in adjuvant therapy that emerged when looking at grade II and

grade III tumours separately were likely due to different treatment regimens based on tumour and patient characteristics in the two age groups (22-24).

8.4 Complications

General complications within 30 days of surgery mostly occurred following resection. The observed frequency of both general complications and postoperative outcome (focal neurological complications) were not found to be significantly different in the older and younger group, even when we removed the potential dilution effect of biopsy, analyzing resections separately. A recent study found more focal neurological deficits in older (>60 years) LGG patients undergoing resection compared to young patients (30) and the reason this study found an insignificant difference (albeit a general trend towards more focal deficits in the old group) may be attributable to a smaller sample size in this study.

8.5 Outcome

Our survival analysis adjusted for age, KPS, gender and tumour size demonstrated a significantly impaired survival in the older group. Worse outcome for elderly patients in this study do not seem to be due to different tumour biology according to traditional glioma classification or treatment-related factors such as chemotherapy or radiotherapy. However, older patients had more IDH-wildtype tumours, and our multivariable model including molecular markers reduced the impact of age, albeit older age was still a negative prognostic factor. Hence, age seems to offer prognostic data beyond molecular data. Our aim in the future is to catalogue all the patient's molecular data to get a more holistic view of how genetic tumor biology is distributed between the groups. We also intend to present a more complete reflection of the radiological data with information about tumor location, tumor eloquence and extent of resection in the near future.

8.6 Strengths and limitations

The main limitation of this study is the absence of a complete set of molecular markers. The recent emergence of molecular profiling in glioma diagnosis is still in its infancy, this meant that only 42 patient's treated between 2010-2016 had their tumours tested. The reclassification for the purpose of studies in lower-grade gliomas further added 28 patients with molecular information. Another limitation is this study's lack of radiological data. The retrospective nature of this study also represent a major methodological challenge with respect to sensitivity for certain measures, interpretation, bias by indication (45).

A major strength of this study were the reasonable long follow-up that is needed to assess clinical outcomes in lower-grade gliomas. Also, we have no loss to follow-up and great accessibility of patient's medical records. Consequently this study has very small amounts of missing data. Other strengths of this study included clinical data collection from the medical records conducted by the same person (author), design of case-report form prior to retrieval of clinical data and mostly an adequate patient population size for statistical analysis (except certain sub group analyses).

This study's exclusion of tumours with radiographic features of glioblastoma could be seen as an example of patient selection bias, however this exclusion likely reduced the effect of diagnostic sampling bias when comparing biopsy and resection.

8.7 Conclusion

Older patients with lower-grade glioma presented more often with deficits compared to younger patients who more frequently presented with seizure. Complications following resection were not associated with patient age. Older patients undergo fewer resections and mapping procedures. The reasons for inferior survival in elderly patients is probably multifactorial, but where baseline and tumour related factors contribute significantly. However, we need more detailed data to conclude on the concern that older patients are inappropriately treated with less aggressive surgery compared to their younger counterparts.

10. Populärvetenskaplig sammanfattning

Elakartade gliom hos äldre patienter

Gliom är den vanligaste hjärntumörsformen i Sverige. Den har en mycket hög dödlighet och eftersom det är relativt många unga patienter som drabbas så är det den cancerform som resulterar i mest förlorade levnadsår. Gliom av grad II och grad III är elakartade tumörer som växer infiltrativt och relativt långsamt inuti den normala hjärnvävnaden innan de omvandlas till den mest elakartade tumörformen, glioblastom (grad IV) och resulterar i död.

Symptomen vid gliom beror på tumörens lokal inuti hjärnan samt dess storlek och växtsätt. Ett epileptiskt anfall är det vanligaste symptomet som patienterna debuterar med innan man kan upptäcka tumören med hjälp av magnetkameraundersökning. Behandlingen utgörs av kirurgi, strålning och cellgifter i olika kombinationer. Behandling syftar till förlänga överlevnaden med så bibehållen livskvalitet som möjligt.

Eftersom gliom är så förknippat med unga patienter så finns det sparsamt med forskning som har inriktat sig på gliom hos äldre patienter, denna studie syftade därför till att undersöka hur denna aggressiva hjärntumörsform och hur dess behandling skiljer sig mellan unga och äldre patienter.

Studien visade att äldre patienter debuterar med andra symptom än yngre patienter, vi såg att äldre patienter oftare drabbas av rörelsenedsättningar och kognitiva nedsättningar medans det var vanligare med endast epileptiska anfall hos yngre patienter.

Det framkom en del skillnader i hur de äldre och yngre patienterna behandlades, man såg bland annat att äldre patienter mer sällan fick sin tumör bortopererad utan fick istället oftare endast genomgå ett vävnadsprov jämfört med yngre patienter. Hos de patienter som fick sin

tumör bortopererad såg man också att man använde sig av vakenkirurgiska ingrepp bland äldre betydligt mer sällan. Vakenkirurgi är en resursintensiv teknik där patienten är vid medvetande och samarbetar med kirurgen som därmed kan skära ut maximal tumörstorlek utan att orsaka skador på viktiga delar av hjärnan.

Överlevnaden var betydligt sämre i den äldre gruppen, 20 månader efter patienterna hade blivit opererade så levde endast 60% av patienterna i den äldre gruppen jämfört med 90% i den yngre gruppen. Beror nu detta på att äldre patienter får sämre vård och opereras sämre? Sanningen är troligen mer komplicerade än så och den verkliga orsaken till att äldre patienter överlever kortare och handläggs annorlunda beror sannolikt på underliggande skillnader i hur tumörerna beter sig biologiskt. Ett av de intressantaste fynden i denna studie var att när man testade tumörerna för markörer med underliggande DNA-mutationer så fann man att äldre patienter hade mer aggressiva tumörer. Denna studie kunde ännu inte redovisa exakta lokaler för tumörerna men en del ledtrådar såsom vilka symptom patienterna hade kan tala för att äldre patienter kan ha sin tumör på mer svåropererade platser. Sammanfattningsvis så har äldre patienter annorlunda tumörer och på grund av detta erbjuds äldre annorlunda behandling då det anses inte kunna dra nytta av för aggressiv behandling.

11. Acknowledgements

This project was conducted at the department of neurosurgery at Sahlgrenska academy under guidance from my supervisor Dr. Asgeir Jakola. My warmest gratitude for the support and expertise he has lent me. I would also like to express many thanks to Alba Corell who helped introduce me to the subject and has remained instrumental in the completion of this project.

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13. Appendices

13.1 Case report form

LOW GRADE GLIOMAS, CLINICAL (LGG)					
NAME					
PERSONAL ID-NUMBER (DD.MM.YYYY-XXXX)		**STUDY-ID**			
Primary surgery, date:					
Number of surgery in total:	☐ 1	☐ 2	☐ 3	☐ 4	☐ > 4
Dead before end of follow-up (1.jan 2017)	☐ No	☐ Yes; date:			

SYMPTOMS

☐ Asymptomatic	☐ Headache/vomiting ("trycksymptom)
☐ Seizure	☐ Motor deficit
☐ Language deficit/disturbances	☐ Visual deficit/disturbances
☐ Cognitive changes	☐ Other: _____

Presence of deficit: ☐ No ☐ Some ☐ Moderate/major

Symptom duration: ☐ < 30 weeks ☐ ≥ 30 weeks

KARNOFSKY SCORE AT TIME OF DIAGNOSIS

Score	Meaning regarding level of function
100 ☐	Normal. No symptoms. No signs of disease.
90 ☐	Able to carry on normal activity; minor signs of symptoms or disease.
80 ☐	Normal activity with effort; some signs or symptoms of disease.
70 ☐	Cares for self; unable to carry on normal activity or to do active work.
60 ☐	Requires occasional assistance, but is able to care for most of his/her personal needs.
50 ☐	Requires considerable assistance and frequent medical care.
40 ☐	Disabled; requires special care and assistance.
30 ☐	Severely disabled; hospital admission is indicated although death not imminent.
20 ☐	Very sick; hospital admission necessary; active supportive treatment necessary.
10 ☐	Moribund; fatal processes progressing rapidly.
0 ☐	Dead.
Unknown	Not shown up to control or not possible to decide from the existing documentation.

ADDITIONAL TESTING, STUDY INVOLVEMENT AND SO ON

Speech therapist assessment preoperative: ☐ Yes ☐ No ☐ Unknown

Navigated transcranial magnetic stimulation: ☐ Yes ☐ No ☐ Unknown

Neuropsychology assessment: ☐ Yes ☐ Yes, but preoperative only ☐ Yes, but postoperative only ☐ No ☐ Unknown

PRIMARY SURGERY

Surgeons:

Type of procedure

☐ Resection ☐ Open biopsy ☐ US-guided biopsy ☐ Navigation biopsy ☐ Stereotactic biopsy

Tools used for resection

☐ Ultrasound ☐ Neuronavigation ☐ 5-ALA ☐ Motor mapping asleep ☐ Awake mapping

Surgical technique for resection

☐ Subpial dissection ☐ ultrasonic aspirator ☐ Microneurosurgery ☐ Unknown (too crude description)

COMPLICATIONS

POSTOP COMPLICATIONS WITHIN 30 DAYS, SCORE MOST SEVERE

☐ Grade Ia, no drugs

☐ Grade Ib, drugs

☐ Grade IIa, intervention without general anaesthesia

☐ Grade IIb, intervention under general anaesthesia

☐ Grade IIIa, Single organ failure, ICU

☐ Grade IIIb, Multiple organ failure, ICU

☐ Grade IV, death

☐ Medical complications

☐ Surgical complications

List all complications:

POSTOPERATIVE OUTCOME (3 months as a difference between transient and permanent)

☐ Motorical	transient	or	permanent	severe	or	non-severe
☐ Language	transient	or	permanent	severe	or	non-severe
☐ Cognitive	transient	or	permanent	severe	or	non-severe
☐ Visual	transient	or	permanent	severe	or	non-severe
☐ Cranial nerves	transient	or	permanent	severe	or	non-severe

☐ Forverring av krampesituasjonen/ Worsening of cramps

☐ Rehabilitation postoperative (yes)

REPORTED TO NATIONAL QUALITY REGISTRY (INCA) ON COMPLICATION

☐ Correct information

☐ Complications that occurred, but reported as no complications to INCA

Describe discordance: _____

☐ Complications did not occur, but reported complications to INCA

Describe discordance: _____

HISTOPATHOLOGY AND MOLECULAR MARKERS

Histopathology (WHO 2007 criteria):

☐ Astrocytoma ☐ Oligoastrocytoma ☐ Oligodendroglioma ☐ Uncertain

☐ Grade II ☐ Grade III

Molecular markers

IDH mutation: ☐ No ☐ Yes ☐ Not assessed

1p19q codeletion: ☐ No ☐ Yes ☐ Not assessed

PROGRESSION/TRANSFORMATION

CLINICAL PROGRESSION (RANO criteria) AFTER PRIMARY SURGERY

☐ Yes, date;_____

- Clear clinical progression that can´t be explained by other causes than tumour or tapering of steroids
- Missing meeting up to control due to death or clinical worsening, unless its caused by documented not related causes/conditions.

☐ No

WHAT CRITERIA FOR PROGRESSION/TRANSFORMATION (RANO definition):

(1) Development of new lesions or increase of enhancement (radiological evidence of malignant transformation)
(2) An 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events
(3) Definite clinical deterioration not attributable to other causes apart from the tumour, or decrease in corticosteroid dose
(4) Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

ADDITION
(5) A histopathological transformation without any confirmed progression

ADJUVANT TREATMENT (BEFORE any repeated surgery)

CHEMOTHERAPY (type)	RADIATION (FRACTION, NUMBER OF FRACTIONS, MODALITY)
START MONTH/YEAR:	START MONTH/YEAR

FIRST REPEATED SURGERY

☐ YES, date;_____

☐ No repeated surgeries before 01.01.2017

Histopathology from repeated surgery:

Molecular markers:

☐ IDH mutation ☐ 1p19q codeletion ☐ MGMT hypermethylation ☐ Not assessed

ADJUVANT TREATMENT AFTER REPEATED SURGERY

CHEMOTHERAPY (type)	RADIATION (Fraction, number of fractioning, modality)
MONTH/YEAR	MONTH/YEAR

13.2 Flow-chart detailing exclusion process