Retrospective Study of High Grade Astrocytoma “Stupp Treatment” Outcome at the Örebro University Hospital

VERSION 1

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Abstract

Background: Glioblastoma is the most common malignant primary brain tumor in adults. It is a serious and lethal tumor that affects yearly affects 4 in 100 000 in Sweden and its median survival is around 12 months. Age at diagnosis is a significant factor that affects prognosis negatively, and patients are generally between 65 and 84 years old. In 2005, a study led by Roger Stupp introduced a technique of treatment consisting of radiotherapy with concomitant temozolomide that became standard treatment for glioblastoma patients. Sweden also has standard treatment recommendation that are published with lead times that are expected to be followed.

Aim: A retrospective quality study was performed. The goal was to study the survival of the glioblastoma patients in USÖ (Örebro University Hospital) and use the numbers published by the 2005 Stupp et al study as a reference. The lead times under the treatment were to be compared to the national recommendations.

Methods and Material: USÖ had 31 patients who underwent “Stupp treatment” between January 2010 and November 2015. The mean age was 62 years old. The patients were identified from the treatment registry of the radiotherapy department at the department of Oncology at USÖ. Molecular analysis of O6-Methylguanin-DNA-Methyltransferase and LOH (Loss of heterozygocy) were also gathered for the study of prognosis. The lead time between diagnosis and surgery, and between surgery and start of oncologic therapy were gathered.

Results: The median survival of the patients was 14.7 months (95% = CI (confidence interval) 8.20 – 19.93) and 2 year survival was 29% (95% CI, 19 – 42%). In the 2005 Stupp et al. study, the median survival was 14.6 month (95% CI, 16.2 – 13.8 %) and the two year survival rate 26.5% (95% CI, 21.2 – 31.7%). 34.6% of the eligible patients had a time under or equal to the recommended lead time between surgery and start of treatment. 24% of the eligible patients had a time under or equal the recommended lead time between diagnosis and surgery.

Conclusion: The survival rates showed results similar to the 2005 Stupp et al. study. This study showed that USÖ has the expected results in terms of survival. The small cohort can be a factor of variability. The lead time are nonetheless generally not respected with less than 30% of the patients in the recommended time intervals. It can be improved on this point. On the other hand, it doesn’t seem to affect survival drastically.
Abreviations:

CI: Confidence Interval
CT: Computer Tomography
GBM: Glioblastoma Multiforme
G-CIMP: Glioma CpG Island Methylation Phenotype
HGG: High Grade Glioma
IDH: Isocitrate Dehydrogenase
IGP: Immunology, Genetics and Pathology
LOH: Loss of Heterozygocity
MGMT: O\textsuperscript{6}-Methylguanin-DNA-Methyltransferase
PS: Performance Status
STUPP: Swiss Oncology professor who led a study on the treatment of Glioblastoma in 2005
USÖ: Örebro University Hospital (UniversitetsSjukhus Örebro)
WHO: World health Organisation
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1. Introduction

1.1. Glioblastomas and other high grade astrocytomas

Glioblastoma is the most common malignant primary brain tumor in adults (1). It is a type of astrocytoma, a tumor originating from astrocytes, cells from the brain glia that are the neural support tissue. Astrocytomas exist in different variations and are classified depending on their malignancy from Grade I to IV. Anaplastic astrocytoma are graded III and Glioblastomas are graded IV (2). The WHO (World Health Organization) classification is based on the aggressivity of the tumor cells, with four parameters that together will classify an astrocytoma as grade IV Glioblastoma multiforme (GBM): nuclear atypia, rapid mitosis, vascular endothelial proliferation, and cellular necrosis. Cells are highly pleomorphic and have aberrations like multinucleated cells. Apart from one of the criterias, not much discerns grade III and grade IV astrocytoma histologically, if not the amount of cellular aberration. The grade III astrocytoma is less frequent and less aggressive, but typically evolves into glioblastoma within a few years. The development of lower grade astrocytomas into glioblastomas is not common, as the grade IV tumor is de novo in 95% of cases (3).

1.2. Epidemiology

In the western world, the glioblastoma incidence is around 4/100 000 and is diagnosed mostly later in life, with a median onset around 64 years of age. Incidence rates are as low as under 1/100 000 before the 35th birthday but increase with age. Between ages 65 and 84, the incidence rate is relatively high (13.09 – 15.03/100 000) (4). After diagnosis, the median survival is generally around 12 month, and only a few patients live two years, even with the best prognosis possible. It is hard to predict the course of the disease for each individual, but the five year survival rate is less than 4% for 55+ years old, and gives an idea of the severity of the condition (5). The etiological factors are unclear. Studies show an interest in the possible effects of cellphone waves on the origin of brain tumors (4).

1.3. Symptoms and diagnostic procedures

Symptoms tends to be neurological. Acute hospitalization often involve seizures, sudden language impairments or hemiparesis. Sometimes symptoms are more progressive and
discreet, as in personality changes or memory deficit (3,6). Symptoms depend greatly on which area of the brain is affected by the tumor. The symptoms are caused by the compression of the brain tissue by tumor growth and peritumoral edema (3). After the upcoming of one or several of these symptoms, imagery is used to identify the location and characteristics of the tumor, and plan for a resection surgery. If resection is not possible (tumor extent, patient age or for health hazard), a biopsy is suggested. A tissue sample of the tumor is very important, in order to obtain a histological confirmation on the diagnosis (2). If a histological information is unavailable, a clinical diagnosis can be made from radiologic features.

1.4. Prognostic factors

Glioblastomas are generally extremely aggressive. Survival depends on the tumor’s response to treatment, and the patient’s ability to endure the difficult treatment. The patient’s age at diagnosis is important to evaluate the patient’s survival under treatment. The 2015 study led by Chen JW shows that the biggest difference in prognosis could be seen in patients under 50 compared to patients who are 50 or older at diagnosis (7). The WHO performance status (PS) gives a score based on the ability to self-sustain of a cancer patient. It is used to assess the patient’s ability to carry on daily activities. It is used as a reflection of the patient’s advancement in the disease, and the capability to endure treatment. It is grading from 0 (healthy, free from symptoms) to 5 (Death). The lower the PS, the better the prognosis is. Furthermore, the MGMT (O⁶-Methylguanin-DNA-Methyltransferase) gene encodes for an enzyme detoxifying Temozolomide, the chemotherapy drug that is used in the Stupp treatment. Therefore, the methylation of the MGMT promotor has a positive effect on prognosis (8). The extent of surgical resection after diagnosis is an important prognostic factor. A total resection is the removal of all visible tumor tissue. Partial resection indicates that parts of the tumor had to be left due to the possible immediate damage on the brain (6). Another important factor are the tumors with Isocitrate Dehydrogenase (IDH) mutations which generally show a better prognosis. These mutations lower the IDHs enzymatic capabilities, and trigger epigenetical modifications that lead to Glioma CpG Island Methylation phenotype (G-CIMP) which is a phenotype showing better prognosis (9).
1.5. Treatment and survival today

Treatment of high grade glioma has always been a difficult field of modern medicine. The severity of the disease makes a cure seldom possible. Prior to 2006, the standard treatment for GBM was radiotherapy, as the chemotherapy drugs showed limited potential to pass the blood-brain barrier without high toxicity, as it was the case for the chemotherapy drug Lomustine. In the early 2000’s, temozolomide became available and showed properties that could be used for treating brain tumors: it is very small (194 Daltons) and is lipophilic. Temozolomide is taken orally and is absorbed in the digestive tract. In the basic pH of the tissue (in the brain for example), temozolomide is hydrolyzed and broken down into methylidiazonium ion. The ion methylates guanine residues in the DNA molecule, forming O\textsuperscript{6}-methylguanin. These changes in the DNA produce single and double breaks in the strand when DNA mismatch repair enzymes try to excise the changes. This causes the apoptosis pathway to be activated (10). In 2005, a study led by Roger Stupp, professor of Oncology in Zürich, published and introduced a new way of handling HGG patients. The study showed that patients treated with radiotherapy and concomitant temozolomide followed by 6 monthly courses of temozolomide as a single agent had significantly improved survival compared to radiotherapy alone (5,6).

The above treatment (ad modum “Stupp” or Stupp treatment) has become a standard of care for glioblastoma patients in modern oncology. The recommended treatment for younger patients with HGG in Sweden follows the plan of treatment with temozolomide concomitant with radiotherapy followed by 6 courses of temozolomide as a single agent (11). The treatment consist of radiotherapy in 2Gy fractions given five times a week for 6 weeks to a dose of 60Gy, with concomitant temozolomide 75mg/m\textsuperscript{2} as a daily dose followed by 6 courses of temozolomide 150-200mg/m\textsuperscript{2} as a single agent five consecutive days in a 28 day schedule (5). There are contra-indications if the patient is over 70 or if the patient has a performance status above 1. For these patients the recommended treatment is palliative radiotherapy to 34Gy (in ten fractions) or the use of temozolomide alone in standard doses (11).

1.6. Aim

The main point of this study is to compare the USÖ Oncology department’s results with the 2005 study led by Roger Stupp in terms of survival of glioblastoma patients.
Moreover, the guidelines of the Swedish National Healthcare Instructions of 2015 has a set of recommended lead times that will be compared with the ones in our patient material.

2. Methods and materials

This project is a retrospective study of the HGG (High Grade Glioma) treatment in Örebro with a comparison to the 2005 Stupp study. The patients diagnosed with a grade III or IV astrocytoma between January 2010 and November 2015 were identified from the treatment registry of the radiotherapy department at the department of Oncology, USÖ. Patients who had received a treatment with radiotherapy and concomitant temozolomide following the Stupp technique after diagnosis were kept for the study. All patients kept for the study received the standard 60Gy dose in fractions of 2Gy once daily five times a week, and received in parallel 75mg/m² of temozolomide (Temodal). Of the 53 patients diagnosed with Grade III or IV astrocytoma, 31 underwent this treatment and were eligible for the study. All information about patients were from the medical journal system at the hospital. The primary goal was the overall survival and the time between diagnosis and beginning of treatment. The second aim of this study is to compare lead times with the recommended guidelines.

2.1. Patients

The eligible patients were aged from 21 to 82 when diagnosed. The material consists of 13 women and 18 men. The patients in the study have all received Stupp treatment as described above. All the patients underwent resection or biopsy at the Uppsala hospital and the tumor material was analyzed at the Uppsala Immunity, Genetics and Pathology (IGP) department. The information gathered was prognostic information similar to the one gathered in the Stupp study. The information collected was the age and gender of the patient, performance status (WHO), the surgery date and the extent of surgical resection, histological data with regard to tumor type (according to WHO classification), IDH, MGMT and LOH 1p 19q.

2.2. Survival

The comparison was primarily on the overall survival of the patients with high grade glioma. The overall survival is measured as the time from the date of diagnosis to the
date of death. The date of diagnosis is set as the first surgical intervention (biopsy or resection).

2.3. Histology and prognosis

The information about the histology was collected from the hospital pathology reports of Uppsala. The MGMT gene is marked positive if methylated, and negative if not methylated. The IDH is marked positive if the gene is mutated and negative if not. The two LOH genes were studied together, and their deletion is reported as a pair. If the gene LOH 1p or 19q was deleted, it is reported as positive and negative if the gene was not deleted.

2.4. Stupp Study

The survival rates in the Stupp study have been compared to the ones in Örebro. To compare the survival in a similar way, the prognostic characteristics from the 2005 Stupp et al. study (Age, extent of surgery...) were used as a reference and the same characteristics were collected from the journal system at USÖ. These characteristics can be found in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1 : Patient Characteristics</th>
<th>(n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE .yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
</tr>
<tr>
<td>Range</td>
<td>21-75</td>
</tr>
<tr>
<td>AGE .no (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>26 (83.9)</td>
</tr>
<tr>
<td>SEX-no (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (58)</td>
</tr>
<tr>
<td>EXTEND OF SURGERY .no (%)</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Debulking</td>
<td>27 (87.1)</td>
</tr>
<tr>
<td>Partial resection</td>
<td>10 (32.2)</td>
</tr>
<tr>
<td>Complete resection</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>unknown extent of debulking</td>
<td>11 (35.5)</td>
</tr>
<tr>
<td>Unknown surgery</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>TIME diagnosis to therapy .wk</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>1.86-9.29</td>
</tr>
<tr>
<td>PATHOLOGICAL FINDING (%)</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>22 (70.9)</td>
</tr>
<tr>
<td>Grade III Anaplastic astrocytoma</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>inconclusive</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>
2.5. Lead time

The standard treatment process has clear guidelines when it comes to time between stages of treatment. For suspected grade III and IV glioblastomas, the time between the initial suspicion and the beginning of the treatment should be 48 days. The day of treatment start is the first day of radiotherapy. The course of treatment is divided in different stages, or Blocks. Block B represents the first CT scan (Computer Tomography) with or without contrast with an intention to diagnose. Block G is the tumor removal surgery, with the intention to remove as much as possible, followed by an analysis of the removed tissue for molecular and cellular diagnosis. The time passed between Block B and block G was gathered and compared to the recommended time of 14 days. Similar procedure was used between the block G and the start of the radiotherapy and was compared to the recommended time of 28 days (12). The national recommendations require to have at least 80% of the patient’s lead time to be under or equal to the recommended time.

![Figure 1: Chronological figure of the treatment process with focus on the studied lead times](image)

3.6. Statistics

The analysis and statistical calculations were done using Excel 2013. The Kaplan-Meier graphic was done using the Kaplan-Meier add-on for Excel 2013. The Kaplan-Meier was used to estimate overall survival of the glioblastoma patients.

3.7. Ethical consideration

In order to achieve the objectives of this study, it has been necessary to go through information in the medical journal system. It is sensible data that the health system is obligated to keep secret, in the exception of the concerned healthcare team. It is very restricted information. Nevertheless, in the name of studies and research, it is possible to obtain very sensible and specific information. Students who are not part of a care team, not
involved in the patient’s treatment, and not even health professionals can in this way have access to the information under heavy secrecy.

It is mandatory to have an authorization from the clinic as to avoid possible lawsuits. The patient can oppose him or herself to the access of the medical files if it feels uncomfortable to have the information in a study. That is a right.

On the other hand, in the case of a deceased patient, it is impossible to know if the “intrusion” in the medical files is welcome or not. The patient can no longer oppose the access to the files.

In this study about glioblastoma, it was particularly relevant as most of the patients that were involved were deceased and could not say their word in this matter. Maybe some of them would have wanted to protect the memories of them by blocking the access to the sensitive information they wouldn’t want to be remembered with.

The study was made with gratitude and in the highest respect to secrecy.

3. Results:

3.1. Survival:

The date of the first surgery was missing for 4 out of 31 patients. 2 of them did not have any information concerning the date of the surgery. As a replacement, the diagnosis date used was the date of the first time the tumor was noticed and mentioned using imagery. It was done that way to have a precise point in time where all the care teams knew it was a brain-tumor patient, and had to follow the standard procedures accordingly. The 2 others had a month and year of surgery written down, but no specific date. In this case, the date was rounded up to the 15th of that month to minimize inaccuracies. For both cases, the uncertainty should be less than 15 days.

The median survival of the patients was 14.7 month from the days of diagnosis to the date of death (95% CI 8.20 – 19.93 month). After two years of treatment, 9 patients survived out of 31. The 2 year survival is 29% (95% CI 19 - 42 %)

In the 2005 Stupp et al. study, the median survival of concomitant temozolomide was 14,6 month (95% CI 16.2 – 13.8 month) and the two year survival rate 26.5% (95% CI, 21.2 – 31.7) (5). Figure 2 is a Kaplan-Meier survival estimation made with the survival data. In a comparative purpose, Figure 3 is the Kaplan-Meier graph found in the 2005 Stupp et Al. study.
3.2. Lead time:

5 out of 31 patients had missing information for the study of the lead time between Block G (surgery) and the start of the treatment. The date of the treatment start was missing for 3 patients. For 1 patient, the date of the surgery was missing. For the 5th patient, both the treatment start and the surgery dates were missing. These patients were not eligible for the study of lead time.
The median time between diagnosis and start of treatment is 33 days (95% CI 28.43 – 38.57 days). 9 patients out of the eligible 26 (34.6%) had a lead time under or equal to the recommended time of 28 days between block G and the treatment start.

6 out of 31 patients were not eligible for the study of the lead time between block B and G. 4 patients were missing a date of operation. 2 Patient were missing a pre-operative image (and a date).

The median time between Block B and Block G (surgery) is 23 days (95% CI 16.57 – 29.43). 6 out of the 25 (24%) eligible patients had a lead time under or equal 14 days between Block B and Block G.

3.3. Histology and prognosis

The histological and genetic information about LOH 1p 19q, IDH and MGMT were gathered and can be found in table 2. The analysis of IDH was done on 15 patients (48.4%), LOH analysis was done on 5 patients (16.1%) and MGMT analysis was done on 6 patients (19.6%) out of 31.

The low amount of patients who underwent the histocytological analysis led to believe there would be a low reliability in analyzing them separately. It was decided there were not enough patient who underwent each analysis to accurately compare them in this study or with another study. The Table 2 contains the results found for each test, if it was positive or negative.

<table>
<thead>
<tr>
<th>PAD RESULTS pos+/neg- .no</th>
<th>IDH pos/neg</th>
<th>LOH genotype</th>
<th>MGMT pos/neg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDH +</td>
<td>LOH 1p+ 19q +</td>
<td>MGMT +</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>IDH -</td>
<td>LOH 1p+ 19q -</td>
<td>MGMT -</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

4. Discussion

This study has the aim to sum up the high grade astrocytoma “Stupp Treatment” outcome at USÖ. The results showed that the overall survival was similar to the results of the Stupp study. The results also show that the lead times can be improved.
The study showed a similarity in the survival results with the 2005 Stupp et al. study. Similar results were found concerning overall survival and 2 year survival. Nevertheless, the confidence interval of this study’s results are larger and reflects the smaller size of the patient sample. The patients in this study tend to be older (median age 62 compared to 53 in the 2005 study). It has been established that age at diagnosis is a negative factor on the survival of the patients (7). It is interesting to stress that similar survival results were met, even though the patients were older at diagnosis in this study.

The study of the lead times in Örebro showed a difficulty to respect the required time between the different stages of treatment for the high grade astrocytoma. Most of the patients waited longer than they were supposed to. The two studied time periods, between Block B and G, and between Block G and treatment start, had lead times longer than expected. The low amount of patients is probably of lesser significance in this result, as the lead time is a more local study, specific to the patients of USÖ. This study shows that most of the high grade astrocytoma patients since 2010 had to wait more than the expected time between each phase of the treatment. The results show that the Oncology department has difficulties respecting time expectation around the surgery phase of the treatment. It could be explained by the requirement to perform the surgery in another hospital than USÖ, as the hospital does not perform the glioblastoma resection surgery there, but in Uppsala for most of the patients in this study. This could be a logistical setback, reflecting itself in the longer lead times around the surgery.

The survival shows good results similar to the ones in the 2005 Stupp et al. study, even though the following of lead times can be improved. Maybe the effort on getting the lead times shorter could lead to an improvement in survival.

The study of histological and genetic information for prognosis were not directly relevant for this study on survival. As it is a new technique, only a few of the patients had undergone the tests under the timeline of the study, as it is shown in table 2. On the other hand, they show that this field of medicine is under constant evolution. These results indicate the possible future study of survival and prognosis including these factors.

4.1. Strengths:

The study cohort may be limited, but its restricted geographical spread makes the studied group very homogenous. The study is local, monocentric and very specific to the
region, minimizing environmental changes between patients.
The study was also led by a small team who made the review. No part of the review work was
done by someone outside of the study. This makes the study more homogenous and exempt it
from differences in protocol between each part.

4.2 Limitations:

There are a few differences between the 2005 Stupp et al. study and this one. The 2005 study was a prospective study and followed the patient as they were under
treatment, whereas in this study, the numbers and data are gathered retrospectively.
The study is spread out on the information gathered over 4 years, from 2011 to 2015. It can
mean differences in approaches and techniques over the years that can affect the different
patient’s treatment. It would be a factor of differences in treatment between patients treated in
2011 compared to 2015 as prognostic and medical technology advances. For example, the
acellular receptors and genetic research wasn’t used as extensively in 2011 in Örebro when
diagnosis were established and it may have affected the decision of treatment. In short, the
longer the time span between patients, the more chances there are differences in the treatment
of patients. This involves changes in parts of the treatment that aren’t the main focus in the
study.
Secondly, there is a sample size difference in the two studies. The Stupp study is international
and gathers over 500 patients, while in Örebro, only 31 patients are available for comparison.
It shows in the study with larger confidence intervals. It probably lowers the power of the
study, though no power calculation was made. High grade astrocytomas are relatively rare and
it can be hard to find statistical power in local studies of the disease.

5. Conclusion

The outcome of high grade glioblastoma patients in Örebro show similarities with
the results of the 2005 Stupp et al. survival study. The patients show similar overall survival
and two year survival. It justifies the use of the “Stupp treatment” over previous ways of
treating high grade astrocytomas. The lead times are on the other hand not followed as strictly
as required. The patients wait longer than recommended before and after resection surgery. A
better following of the lead times might improve the survival rates. It lifts a problem that
should be addressed. The treatment of such an aggressive tumor form should respect the official lead times to give the patient the best result possible. Even though the lead time was greater than recommended it doesn't seem it had any negative effect on the outcome of the treatment for these patients.

6. Acknowledgements

I would like to thank my two mentors, clinical mentor David Löfgren and scientific mentor Ann CHARLOTTE Dreifaldt for the guidance and advice throughout the project. Thank you for all the constructive criticism you gave me. I would also like to thank my father for the proofreading and advices given in the toughest times. I would also like to express my gratitude to all who helped and supported me during the whole process.

7. References


