# Pediatric Neuro-oncology in Small Centers – Quality Control of Network Support: The HIT-GBM Experience

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**Abstract.** *Background: The quality of care for children with brain tumors might be higher in large medical centers; however, it may be possible to improve the quality of care received in smaller centers if they join an effective network. Aim: This study used the HIT-GBM® database to compare the quality of care provided to pediatric high-grade glioma and diffuse intrinsic pontine glioma patients among various medical centers of differing sizes. Patients and Methods: Overall survival was used as a defining parameter. Indirect measures were the time intervals between the first clinical signs of cancer, initial diagnostic imaging, surgery, or chemotherapy and radiation. Results: From 1995 to 2003, 310 children (137 girls and 173 boys, aged 3 to 18 years old) were registered from 72 medical centers in Europe. Center sizes differed from 1 to 17 registered patients. Center size did not affect survival, nor any of the time intervals studied. Conclusion: There was no evidence that the quality of care differed between smaller and larger centers.*

The benefit of multicenter groups is well established in pediatric oncology (1), but the question of whether smaller medical centers networking in these groups can match the quality of care provided in larger centers remains debatable. Larger hospitals are able to provide more specialized services (1, 2), yet it might be argued that smaller centers are able to provide more personalized care, and that networking provides access to offsite specialists. Such assumptions and arguments should be validated by objective studies (3).

The term 'high-grade glioma' (HGG) encompasses a variety of diagnoses, including glioblastoma multiforme World Health Organization (WHO) grade IV, anaplastic astrocytoma WHO III, and others. The overall survival (OS) rates for children with HGG are only moderately higher after complete surgical tumor resection (4), radiation and chemotherapy (5, 6). Diffuse intrinsic pontine gliomas (DIPG) are astrocytic tumors, which only rarely are treated with surgical procedures. Radiation therapy has been demonstrated to prolong progression-free survival, but the role of additional chemotherapy is debatable (7). For these diseases, death is still a frequent outcome, and survival times define the quality of care. Recently, 'process quality' was proposed as a means of assessing the quality of healthcare through the measurement of indirect parameters such as the delay between diagnosis and treatment (3, 8), or infection rates, as they are easier to measure and therefore attractive as a quality control (QC) tool. Nevertheless, indirect measures need to be positively correlated to survival before they can be recommended as a reliable QC tool (9).

This study used the HIT-GBM® database to test the hypothesis that the prognosis of pediatric patients with high grade glioma is better when they are treated in larger rather than smaller medical centers and to evaluate possible alternative indirect QC measures.

## Patients and Methods

*Patient data*. The HIT-GBM® study group has enrolled pediatric patients with either HGG or DIPG on a series of treatment trials since 1994. The third protocol (HIT-GBM-C) was the first that showed an improvement over previous treatments (10-12), now

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allowing to further assess factors that influenced the improvement. Appropriate consent forms that were approved by the Institutional Review Board were mandatory.

*Clinical endpoints and center characteristics*. Age at diagnosis was analyzed in three groups: 5, 5-10, and10 years. 'Imaging delay' was defined as the time interval between the first documented clinical sign of cancer and the first positive diagnostic imaging. 'Surgical delay' and 'treatment delay' were the time intervals between the diagnostic imaging and surgery, and the start of non-surgical oncological therapy, respectively. Event-free survival was defined as an outcome that ended with death, tumor recurrence, or second malignancy. Medical center size was defined by the number of patients enrolled, and separated into three groups: five or fewer patients enrolled, six to twelve patients enrolled, or more than twelve patients enrolled. In addition, centers were also classified by population density, as located in an area with less than 500 registered inhabitants per $km^2$ or more (13), and 'centers of major cities' were defined as located in Vienna, Berlin, Hamburg, or Munich, the four largest cities from which patients were registered.

*Statistical analysis*. The distribution of each possible risk factor was described and subgroups were compared using cross tabulations, chi-square tests for qualitative parameters, and explorative Pearson correlations for quantitative parameters. The prognostic relevance of each parameter was determined with Kaplan-Meier estimates and log-rank tests in all of the data as well as in all of the subgroups. These tests were performed in order to detect a possible bias relevant for the conclusion; they were descriptive only. The main purpose of this analysis was to test the hypothesis that patient survival was better in larger centers. In this test, a *p*-value of less than 0.05 was considered significant. The analysis was performed using SPSS, v.12.0 software (SPSS Inc., Chicago, IL, USA).

## Results

*Patients*. A total of 310 patients (173 boys and 137 girls) were registered in the HIT-GBM® database between 1995 and 2003 and followed up until 2005. The age at time of diagnosis ranged from 3.3 to 18.0 years (median 9.9 years). The primary tumor locations were the cerebral hemispheres in 84 patients, thalamus and basal ganglia in 38, pons in 134, brain stem outside of the pons in 14, cerebellum in 14, spinal cord in 8 and multiple overlapping areas in 18 patients. The surgical procedure was reported as a complete resection in 49 patients, subtotal resection in 35, partial resection in 58, biopsy only in 99, and no surgery in 69 patients. A total of 123 tumors were classified as grade IV (WHO), 101 as grade III, and 15 as low grade. No histological data were available in 71 patients. Patients with low grade histology and without histological diagnosis had pontine glioma and were enrolled based on radiographic criteria. The median OS time from diagnosis was 1.02 years (95% CI: 0.91-1.12), and the median event-free survival time was 0.54 years (95% confidence interval (CI): 0.48-0.59). Standard risk factor analysis based on tumor biological criteria and the treatment and toxicity results of the various protocols have been published elsewhere (11).

*Time intervals, process quality*. The imaging delay time was documented in only 129 patients. It ranged from –3 to 1113 days (median: 23 days, a negative value refers to imaging that was performed for a different indication and clinical tumor signs were recognized only thereafter). The median surgery delay was seven days and five patients had a surgical delay of more than 60 days (n=surgical delay time documented: 105 patients). The median treatment delay was 20 days (range: 0-513, n=288). The time delay between initial clinical signs and the initial diagnostic imaging was shorter in the subgroup of patients who developed high-grade glioma as a second malignancy ($p=0.004$), and no patient with a secondary high-grade glioma had an imaging delay of more than 21 days. Patients who underwent the initial imaging within 21 days more frequently had surgery within seven days than patients who had longer imaging delay times ($p<0.0005$). The surgery delay time was predictive of surgical outcome, as surgical procedures within seven days were more likely to be complete resections than were surgeries done later ($p=0.026$ by the Pearson correlation). The longest imaging delay times were found in patients with fibrillary astrocytoma of the pons (four patients, median imaging delay time: 214 days). The times until nonsurgical treatment started were generally longer in the earlier years of study enrollment: early surgery within seven days after imaging was more frequent in the latest protocol ($p<0.0005$).

*Center size and quality of care*. Patients were enrolled from 72 hospitals in Germany, Austria, Switzerland, and Slovenia. The number of patients at each hospital varied from one to 17. Nine hospitals registered ten or more patients, while 21 hospitals registered only one patient. Eighty-one patients were registered at centers located in sparsely populated areas, whereas 34 patients were registered at centers located in major cities. All available risk factors were compared according to center size, and only the patients' gender distribution was unequal in medical centers of different sizes (more girls in larger centers, $p=0.014$). Thus it can be concluded that there was no influence of center size on overall patient outcome. Patients treated in centers that had registered five patients or fewer had a median overall survival time of 1.08 years (95% CI: 0.96-1.21), patients registered in centers that had registered six to 12 patients had a median overall survival time of 1.03 years (95% CI: 0.84-1.23), and patients registered at centers enrolling more than twelve patients had a median overall survival time of 0.96 years (95% CI: 0.71-1.21). This was also true when the total group of patients was divided in subgroups by age, gender, histology or tumor locations, and analyzed separately, or when event-free survival was used as endpoint. There was also no difference in response to treatment or in the indirect parameters when comparing smaller and larger centers, except for one subgroup analysis which showed an apparent shorter surgery delay in centers with less than ten

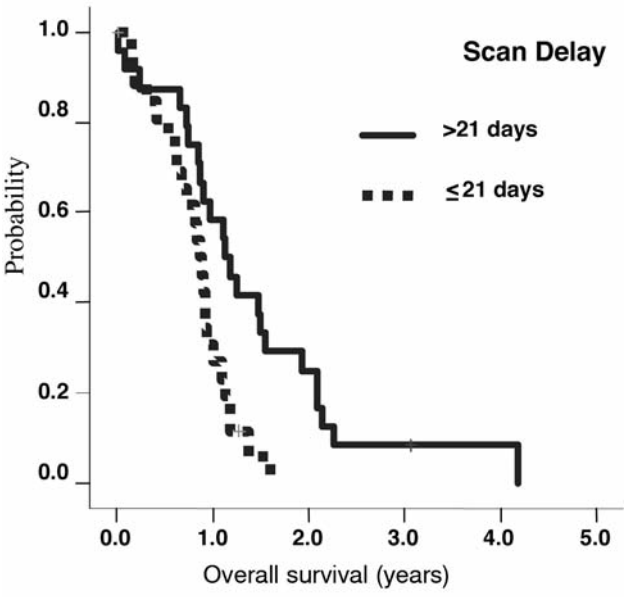


Figure 1. *Effect of imaging delay time on overall survival in patients with DIPGs. Counter intuitively, delay of >21 days was associated with better prognosis. (No delay n=27, censored=2; delay n=24, censored=1, p=0.0048).*

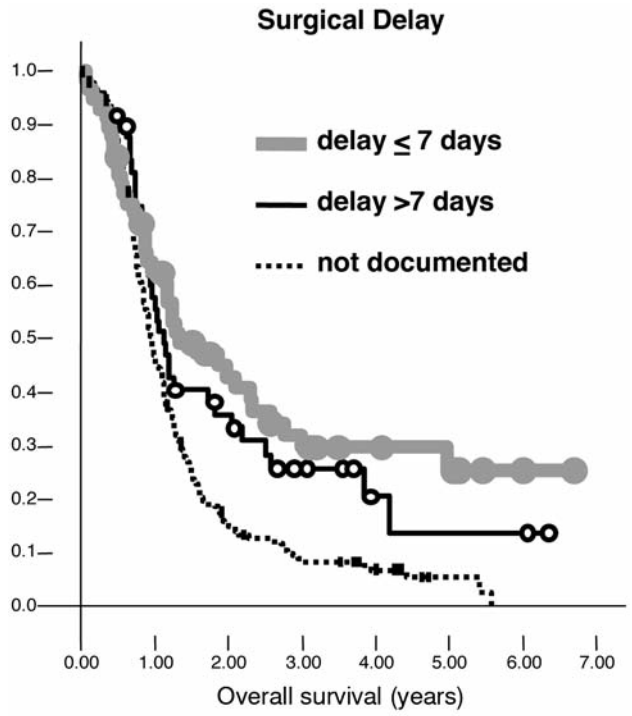


Figure 2. *Effect of surgical delay time on overall survival. (Y-axis: Kaplan Meier estimate of survival). Patients classified as 'not documented' mostly had DIPG, and no surgery. The survival difference between the two other groups is marginally significant. (No delay n=57, censored=19; delay n=48, censored=13; no data 205, censored=17, p<0.0005 for all, but p=0.48 when only comparing delay versus no delay).*

patients registered as compared to larger centers (10.1 days±17 standard deviation *versus* 21.3±30.7 days, $p$=0.019).

*Process quality and outcome*. In the total patient cohort, there was no statistically significant difference in survival time between patients with an imaging delay of longer than 21 days and those with shorter delays. This was different in the subgroup of patients with diffuse intrinsic pontine glioma (DIPG). In those patients, an imaging delay time of more than 21 days was associated with a longer median overall survival time than a shorter delay (median survival: 1.12±0.17 years *versus* 0.87±0.06 years, n: 24 *versus* 27 excluding 81 with insufficient documentations, $p$=0.0048; Figure 1). Although there was no significant association between surgical delay and patient outcome, there was a trend toward improved survival for patients who underwent surgery within seven days of the initial diagnostic imaging (Figure 2). However, patients for whom the treatment (radiation or chemotherapy) delay was longer than 21 days, had a strong tendency toward prolonged overall survival, compared to patients in whom the treatment delay was less than 21 days (median survival: 1.24±0.13 years *versus* 0.95±0.07 years, $p$=0.0525).

## Discussion

In the Authors' opinion, the most important finding of this study was the equal outcome found among smaller and in large medical centers.

Several details of the analysis provided interesting insights in the analyzed healthcare system for pediatric neuro-oncology. Usually, medical centers located in densely populated areas also treat more pediatric patients regardless of the underlying disease. However, for children with HGGs and DIPGs, the centers in Würzburg and Augsburg had the highest numbers of patients, even though these two cities are not located in highly populated areas. Those hospitals are renowned for excellent neuro-oncology programs. The high reputation of the hospitals was the likely cause prompting referral pathways and parents' wishes. Different levels of parents' attention, worries and determination might also explain many of the other findings. For instance, the study found an earlier detection of secondary malignant gliomas as compared to primary tumors, probably reflecting increased vigilance and the use of regular monitoring. Gender-specific behavior of caregivers might explain why more girls were treated in larger centers; this should be tested in other data sets.

The most unexpected observation was the apparently better prognosis for patients with pontine tumors who had longer imaging delays (Figure 1). In general, the presumption is that rapid diagnosis is associated with improved outcome. A

possible explanation is that the underlying biology of the tumors differed, and that patients with more slowly growing tumors develop clinical signs late in the disease process, progressing more slowly and therefore less alarmingly, leading to later imaging yet still longer survival times. This allows one to generate an interesting hypotheses regarding DIPG heterogeneity, possibly providing an argument for using this parameter as an influencing factor when analyzing DIPG data, and against using this parameter for QC.

Treatment delay time was not strongly associated with overall outcome in these data. There was a small but insignificant trend toward longer survival for those patients undergoing initial surgery within seven days of the initial diagnostic imaging, and an opposite tendency for patients who started chemotherapy or radiotherapy early. A possible explanation is the variance of aggressiveness in the neurosurgical approach. After complete resections, the postoperative recovery time, in which chemotherapy could not be started, was longer than in patients who underwent only limited procedures. These results suggest that surgery should not be delayed after the first diagnostic imaging, but they do not support an aggressively short timeline for chemotherapy after surgical resection. The lack of an association between rapid onset of therapy and improved survival also argues against using those parameters to measure QC.

A secondary aim of this analysis was also to identify meaningful but easy-to-use parameters for QC, such as the time from diagnosis to the onset of treatment. These parameters were easy to measure but difficult to interpret and did not yield any more meaningful QC methods.

In conclusion, this study found no evidence that the outcome of pediatric HGG was better in larger hospitals than in smaller hospitals. On the way to this conclusion the analysis uncovered a number of interesting details such as longer survival of pontine glioma patients in whom the diagnostic imaging was performed late, gender-specific hospital choices, and a lack of relevance of indirect quality assurance parameters.

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