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Timing of glioblastoma surgery and patient outcomes: a multicenter cohort study

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Abstract

Background. The impact of time-to-surgery on clinical outcome for patients with glioblastoma has not been determined. Any delay in treatment is perceived as detrimental, but guidelines do not specify acceptable timings. In this study, we relate the time to glioblastoma surgery with the extent of resection and residual tumor volume, performance change, and survival, and we explore the identification of patients for urgent surgery.

Methods. Adults with first-time surgery in 2012–2013 treated by 12 neuro-oncological teams were included in this study. We defined time-to-surgery as the number of days between the diagnostic MR scan and surgery. The relation between time-to-surgery and patient and tumor characteristics was explored in time-to-event analysis and proportional hazard models. Outcome according to time-to-surgery was analyzed by volumetric measurements, changes in performance status, and survival analysis with patient and tumor characteristics as modifiers.

Results. Included were 1033 patients of whom 729 had a resection and 304 a biopsy. The overall median time-to-surgery was 13 days. Surgery was within 3 days for 235 (23%) patients, and within a month for 889 (86%). The median volumetric doubling time was 22 days. Lower performance status (hazard ratio [HR] 0.942, 95% confidence interval [CI] 0.893–0.994) and larger tumor volume (HR 1.012, 95% CI 1.010–1.014) were independently associated with a shorter time-to-surgery. Extent of resection, residual tumor volume, postoperative performance change, and overall survival were not associated with time-to-surgery.

Conclusions. With current decision-making for urgent surgery in selected patients with glioblastoma and surgery typically within 1 month, we found equal extent of resection, residual tumor volume, performance status, and survival after longer times-to-surgery.

Key Points

- In 1033 GBM patients, the time between diagnosis and surgery was not associated with patient outcome.
- Patients selected for urgent surgery had a low performance status and a larger tumor volume.
- With current decision-making, a maximum acceptable time-to-surgery of 1 month seems reasonable.

Importance of the Study

In this study, we relate the time between the diagnostic MR scan to glioblastoma surgery with the extent of resection and residual tumor volume, performance change, and survival, and we explore the identification of patients for urgent surgery in a cohort of 1033 patients from 12 neuro-oncological referral hospitals throughout Europe and North-America. We found equal extent of resection, residual tumor volume, performance status, and survival following longer waiting times. We also found that patients who were selected for urgent surgery had a low preoperative performance status and a large tumor volume. As the vast majority of patients were operated within 1 month from the initial scan, this seems a reasonable maximally acceptable time-to-surgery. This information may reset the standard for when these tumors should be operated along with identification of the patient category for urgent attention of timely surgery.

Upon the radiological establishment of a suspected glioblastoma, patients expect prompt surgery. Neurosurgeons also perceive an urge to avoid delay in time to surgery. Surgery is typically scheduled urgently in younger patients with severe or progressive symptoms as well as in those with considerable mass effect, midline shift, or obstructive hydrocephalus. Some patients with stable symptoms may need more time to decide on treatment options and those with stable or receding symptoms after corticosteroids and smaller tumors may spend time on a waiting list. For many neuro-oncological units limiting resources to schedule surgery include availability of personnel and the capacity on the wards and of the operating rooms.

Moreover, the poor prognosis with a 5-year survival of 6.8%,[1] despite surgery, concomitant chemoradiation, and adjuvant chemotherapy,[2] supports the urge to timely treatment. Practice guidelines have so far not specified what is to be considered timely treatment.[3–7] As a consequence, practice variation in timing of surgery has been observed in large population-based studies evaluating patterns of care in patients with glioblastoma, with surgery within a month varying between 34% and 82%.[8,9]

At the same time, glioblastomas expand before surgery with an average volumetric doubling time of approximately 1 month.[10–12] It is conceivable that tumor growth with further infiltration into functional brain could reduce the extent of resection and increase the residual tumor volume by limiting the barriers of resection, and render performance worse and survival time shorter.[13,14] Results, however, have been conflicting. For example, delayed surgery in patients with glioblastoma, who presented with seizures, was associated with shorter survival in one study,[15] while shorter survival has been observed in another study for patients who had urgent glioma surgery.[16,17] In other cancers such as breast,[18] colon,[19] and lung,[20] shorter survival was observed after longer time to surgery, presumably due to progressive tumor growth.[21]

In this study, we determined the association between the time from the first diagnostic MR scan to surgery and the extent of resection and residual tumor volume, performance status alteration, and survival in patients with glioblastoma. We also explored patient and tumor characteristics as potential selection criteria for urgent surgery.

Materials and Methods

Patient Inclusion

Twelve neuro-oncological care teams participated in this study: Northwest Clinics, Alkmaar, Netherlands (ALK), Amsterdam University Medical Centers, location VU

medical center, Netherlands (AMS), University Medical Center Groningen, Netherlands (GRO), Medical Center Haaglanden, the Hague, Netherlands (HAG), Humanitas Research Hospital, Milano, Italy (MIL)#6 Hôpital Lariboisière, Paris, France (PAR), University of California San Francisco Medical Center, US (SFR), Medical Center Slotervaart, Amsterdam, Netherlands (SLO), St Elisabeth Hospital, Tilburg, Netherlands (TIL), University Medical Center Utrecht, Netherlands (UTR), Medical University Vienna, Austria (VIE), and Isala hospital, Zwolle, Netherlands (ZWO).

Consecutive adult patients with first-time supratentorial surgery for a histopathologically confirmed glioblastoma between January 2012 and December 2013 were included in this retrospective observational cohort analysis.[22] We included both patients with a biopsy and a resection as the type of surgery may contribute to the time-to-surgery. Patients were included for analysis if a preoperative MR scan was available and, in case of a resection, also a postoperative MR scan within 72 h was available. Informed consent was obtained from all patients, and for each participating hospital IRB approval was obtained as required.

Patient Data

Patient information was collected from the electronical medical records. Data consisted of age at time of diagnosis, gender, preoperative, and postoperative Karnofsky performance score before initiation of adjuvant treatment, type and date of surgery, chemoradiotherapy, and date of death or date of last follow-up. We defined performance status as the prospectively collected Karnofsky performance score, and considered it missing otherwise. Patients either underwent a biopsy or a resection. We defined biopsy as tumor removal for only histopathological diagnosis by an open or stereotactic procedure; and resection as the removal of more tumor than necessary for a histopathologic diagnosis.

MR Scan Data

Pre- and postoperative MR scans were collected from the hospitals' archival systems and included 3D T1-weighted images before and after gadolinium, T2-weighted or FLAIR and diffusion-weighted images. Postoperative scans acquired more than 72 h after surgery were not included to avoid misinterpretation of gliosis, early progression, or ischemia as residual glioblastoma.

The diagnostic scan was defined as the first MR scan before surgery that established the radiological diagnosis of presumed glioblastoma. We defined the time-to-surgery as the number of days between the date of the diagnostic scan and the date of surgery. In case of additional preoperative MR scans, the preoperative MR scan was defined as the last scan before surgery. We defined surgery as urgent when performed within 3 days after the diagnostic scan.

Volumetric Measurements

Tumor volumes were acquired by 3D manual segmentation of the tumor on pre- and postoperative T1-weighted gadolinium-enhanced images. A trained rater (DMU) performed the segmentations under supervision of a neurosurgeon (PWH) and neuroradiologist (FBA). Segmentations were done using Brainlab Smartbrush Suite software (BrainLAB AG). We considered gadolinium-enhancing tissue with or without enclosed necrosis or cysts as tumor. On postoperative scans, diffusion-weighted images were used to distinguish postoperative residual tumor volume from surgical effects.

Tumor volume change was assessed by subtracting the tumor volume of the diagnostic scan from the direct preoperative scan in patients with at least 2 preoperative MR scans. We also calculated volumetric doubling times and derived tumor-specific growth rates.[23,24] The volumetric doubling times were calculated as proposed by Yamashita et al.[24]: $DT = \ln 2/(\ln (V_1 / V_2)) \times t$, where DT is the volumetric doubling time in days, V_1 indicates the tumor volume of the diagnostic scan, and V_2 the tumor volume of the preoperative scan after an interval of t days. The specific growth rate (SGR) was derived from the DT as proposed by Mehrara et al.[23]: SGR = ln2/DT (% per day). We created subgroups based on the SGR into patients with tumors that shrank, neither shrank or grew, or grew.[10]

Outcome Measures

As outcome measures, we considered the extent of resection and residual tumor volume, functional outcome, and survival.

The extent of resection was calculated as the percentage of the preoperative tumor volume that was resected. The residual tumor volume was defined as the remaining postoperative tumor volume after resection in mL. We used arbitrary thresholds of 98% for the extent of resection and 3 mL for the residual tumor volume for "gross total resection."[25,26]

Functional outcome was defined as change in performance status after resection which was calculated by subtracting the preoperative from the postoperative performance status. Positive values indicate a performance improvement, negative values a performance decline.

Survival was defined as number of days between the date of surgery and the date of death. Patients were censored at the last date known to be alive or when lost to follow up.

Statistical Analysis

To correlate time-to-surgery with patient and tumor characteristics, we explored associations by time-to-event analysis in Kaplan–Meier curves and with univariate proportional hazard models. Then, time-to-surgery was evaluated in multivariable proportional hazard models with patient and tumor characteristics, and team as random effect.

To compare tumor locations voxel-wise, tumor probability maps were constructed as previously described.[27] In brief, tumor segmentations were nonlinearly registered from the diagnostic scan to the Montreal Neurological Institute 152 1-mm standard brain template and

aggregated. Results were superimposed on the standard brain for anatomical interpretation.

In eligible patients, we visually explored tumor volume change over time-to-surgery in boxplots. We used a nonparametric permutation test with one million randomizations to test for statistical significance without assumptions on probability distributions.[28]

To determine the associations between time-to-surgery and the extent of resection and residual tumor volume, between time-to-surgery and chemoradiotherapy, and between time-to-surgery and performance change we also used permutation tests.

To determine the association between time-to-surgery and patient survival, we plotted Kaplan–Meier curves and evaluated associations in univariate proportional hazard models. Subsequently, time-to-surgery was evaluated as prognostic factor for survival in conjunction with age, preoperative performance status, tumor volume, type of surgery, and chemoradiotherapy in multivariable proportional hazard regression analysis with team as random effect.

To visualize multivariable analyses, we plotted the time-to-surgery against extent of resection, residual tumor volume, performance change, and survival by subgroups according to age, preoperative performance, tumor volume, and type of surgery. We also plotted the time-to-surgery against extent of resection, residual tumor volume, performance change, and survival by subgroups according to tumor growth.

Statistical analyses were performed in R (version 3.4.3; R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2017). *P*-values less than .05 were considered significant.

Results

A total of 1039 patients met the inclusion criteria, of whom 6 patients had MR scans of insufficient quality for segmentation, leaving 1033 patients for analysis.

The overall median age was 63.9 years and 64% patients were males. Preoperative performance status was 70 or higher in 829 (85%) patients. Median tumor volume at diagnosis was 27 mL. The median time-to-surgery was 13 days. Surgery was performed urgently within 3 days in 235 (23%) of patients and within 1 month in 889 (86%). A resection was performed in 729 (71%) patients. The median extent of resection in these patients was 97% and the median residual tumor volume was 1.1 mL. An extent of resection of ≥ 98% and residual tumor volume of ≤ 3 mL were observed in 301 (41%) and 503 (69%), respectively. Postoperative performance status was scored as 70 or higher in 587 (89%) of 655 patients with available information. Of these patients, an unaltered or improved performance was noted in 525 (80%) patients, whereas a deterioration was noted in 130 (20%) patients. Concomitant chemoradiotherapy and adjuvant chemotherapy were administered in 483 (47%), chemotherapy alone in 73 (7%), radiotherapy alone in 103 (10%), no adjuvant treatment in 215 (21%); additional treatment information was unavailable in 159 (15%). The median overall survival was 11.3 months, 5.2 months following biopsy only and 14.2 months following resection. The patient and tumor characteristics and treatment results per team are listed in Supplementary Table 1.

A Shorter Time-to-Surgery for Patients With Lower Performance Status and Larger Tumor Volumes

Patient age was not associated with time-to-surgery (Figure 1A). Patients with a lower performance status (Figure 1B) or larger tumor volume (Figure 1C) had a shorter time-to-surgery. The type of surgery was not associated with time-to-surgery (Figure 1D). A lower performance status (hazard ratio [HR] 0.942, 95% confidence interval [CI] 0.893–0.994) and a larger tumor volume (HR 1.012, 95% CI 1.010–1.014) were independently associated with a shorter time-to-surgery in a multivariable proportional hazards model, whereas age and type of surgery were not associated with time to surgery (Supplementary Table 2).

Time-to-Surgery Was Not Associated With Tumor Location

Tumors were located in the left hemisphere in 505 (49%) patients and in the right hemisphere in 527 (51%). The time-to-surgery was not associated with hemisphere affected. The tumor locations were comparable between time-to-surgery intervals as shown in Figure 2. The known preferential locations of glioblastoma were observed at each time-to-surgery interval, such as the periventricular region, insular cortex, and temporal stem and lobe, with sparse involvement of the occipital lobes. There was no indication for more eloquent locations to have a shorter time-to-surgery.

Time-to-Surgery Was Not Associated With Tumor Volume Change

A subset of 584 (57%) patients were identified with 2 or more preoperative MR scans available to analyze tumor growth. Median tumor volume at the first diagnostic scan was 23 mL and at the last preoperative scan 30 mL. Median volume change was + 3.3 mL. The median volumetric doubling time was 22 days and the median specific growth rate was 1.1% per day. Tumor volume change was similar over time-to-surgery intervals (Supplementary Figure 1).

Time-to-Surgery Was Not Associated With the Extent of Resection and Residual Tumor Volume

The extents of resection and residual tumor volumes were similar across time-to-surgery intervals (Figure 3A and B). An extent of resection of ≥ 98% per time-to-surgery interval was achieved in 108 (42%), 52 (39%), 58 (45%), 34 (40%), and 49 (39%) patients ($P = .80$). A residual tumor volume of ≤ 3 mL was achieved in 171 (66%), 94 (71%), 93 (73%), 58 (69%), and 67 (54%) of patients by time interval ($P = .51$).

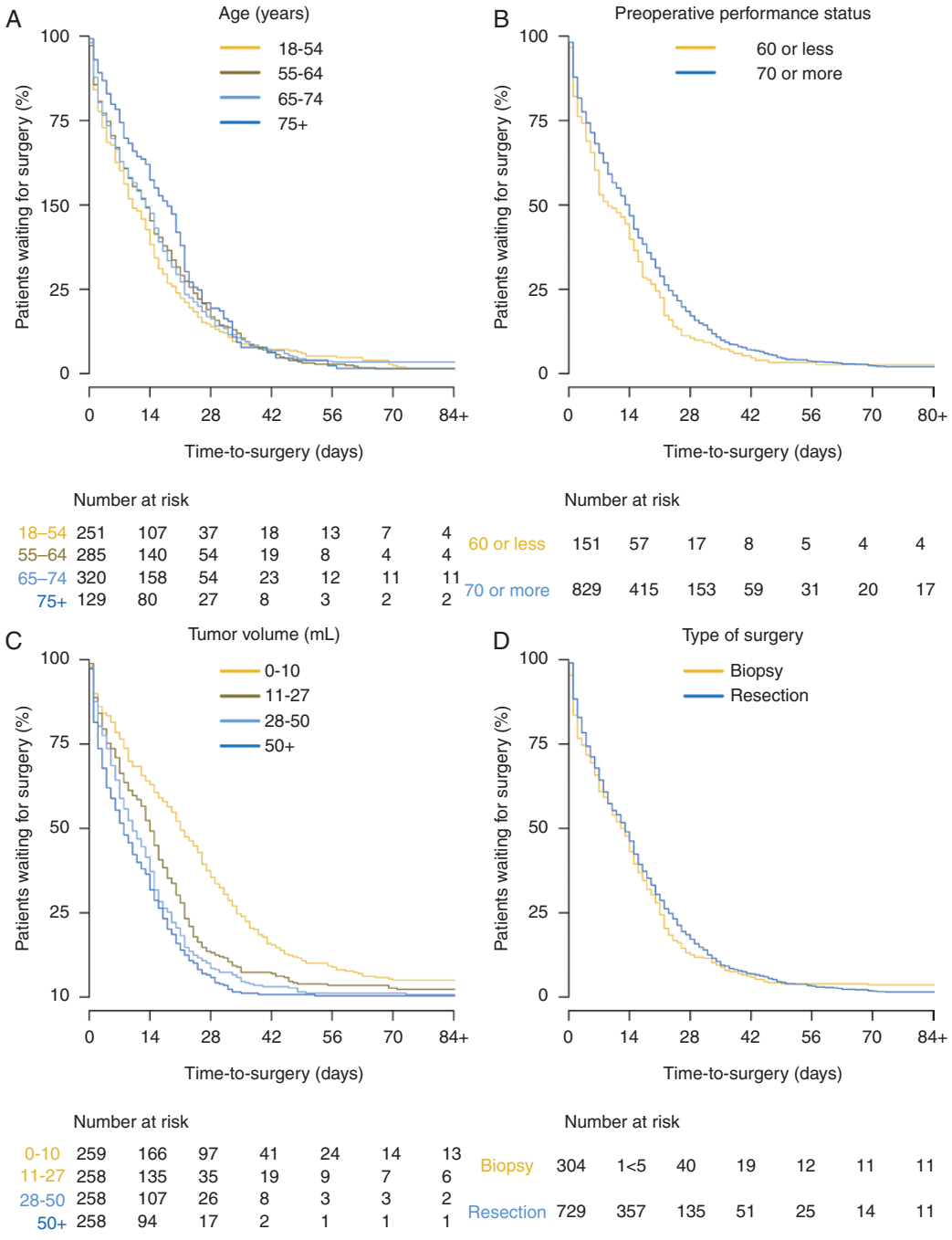

Figure 1. Kaplan–Meier plots of time-to-surgery for (A) age ($P = .21$), (B) preoperative performance status ($P < .01$), (C) tumor volume ($P < .01$), and (D) type of surgery ($P = .38$) for all 1033 patients.

Time-to-Surgery Was Not Associated With Performance Changes After Resection

Changes in performance were similar across time-to-surgery intervals (Figure 3C). Across patients with a resection, a performance decline of 20 or more was observed in 51 (8%) of 655 patients.

Time-to-Surgery Was Not Associated With Chemoradiotherapy

In 483 patients with complete chemoradiotherapy, the median time-to-surgery was 12 days, similar to 15 days in 391 patients with incomplete or no chemoradiotherapy (no significant difference) and as displayed in boxplots in Supplementary Figure 7.

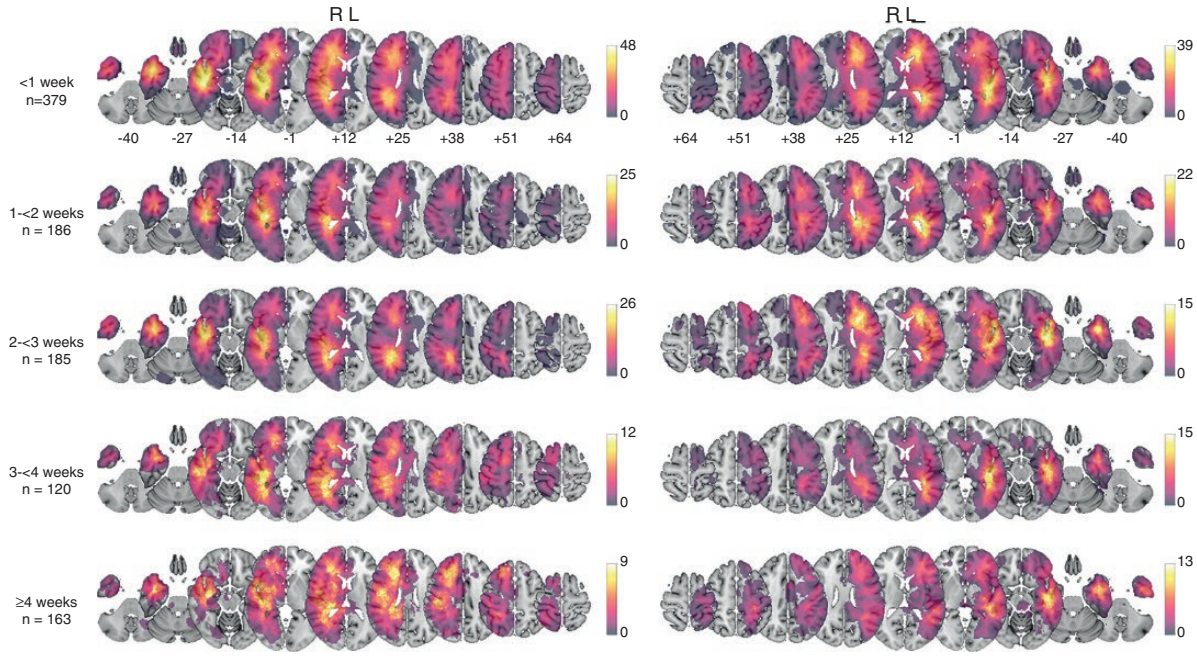

Figure 2. The tumor probability maps for the right and left hemisphere categorized by the time-to-surgery in weeks. The z-coordinates from the Montreal Neurological Institute (MNI) brain template are plotted. The color legends indicate the number of patients with preoperative tumor at a location.

Time-to-Surgery Was Not Associated With Overall Survival

Overall survival was unrelated to time-to-surgery intervals (Figure 4). Time-to-surgery in days was not associated with overall survival in multivariable analysis (HR 1.000, 95% CI 0.999–1.001; Supplementary Table 3).

Subgroup Analysis

A longer time-to-surgery in patients with tumor volumes > 50 mL seemed related with a lower extent of resection and larger residual tumor volume, more frequent performance decline, and a shorter survival (Supplementary Figure 4). None of the other subgroup plots indicated a relation between time-to-surgery and extent of resection, residual tumor volume, performance change, or survival (Supplementary Figures 2–6).

Discussion

The main finding of this study is that time-to-surgery is not associated with patient outcome, in the circumstances of careful surgical decision-making to discern the patients who require urgent surgery from those who can be scheduled electively. Lower performance status and larger tumor volume are characteristics of patients with shorter time-to-surgery. The extent of resection and residual tumor volume, performance change, and patient survival are not associated with time-to-surgery. As the vast majority of patients were operated within 1 month from the initial scan, this seems a reasonable maximally acceptable time-to-surgery.

Several factors may contribute to the time between radiological diagnosis and surgical treatment. Some factors concern the diagnostic process, such as the time to neurological and neurosurgical consultation, anesthesiologic assessment of co-morbidities, tumor board discussions, and additional imaging for surgical planning. Other factors include hospital resources such as personnel and capacity on wards and operating rooms, and competing urgency of other patients for a spot in the schedule for emergency or elective surgery. Other factors relate to patient characteristics such as age, performance and temporary symptom relief by corticosteroids, or to tumor characteristics such as the volume, midline shift, mass effect, and obstructive hydrocephalus.[3] A prolonged time-to-surgery could potentially result in disadvantages to patients, including tumor progression with decreased tumor removal, more complex surgery with higher risk for functional decline, and decreased tumor control with shorter survival. Contrary to observations in other cancer types[29,30] and to our expectations, this was not observed in our data. This can be explained by careful selection of patients who need urgent surgery. Patients with a lower performance status and larger tumor volumes were selected for more urgent surgery.

Interestingly, time-to-surgery was not associated with tumor location, where we expected the time-to-surgery to be shorter for patients with tumors infiltrating eloquent locations due to more frequent or more severe neurological symptoms and worse performance.[31]

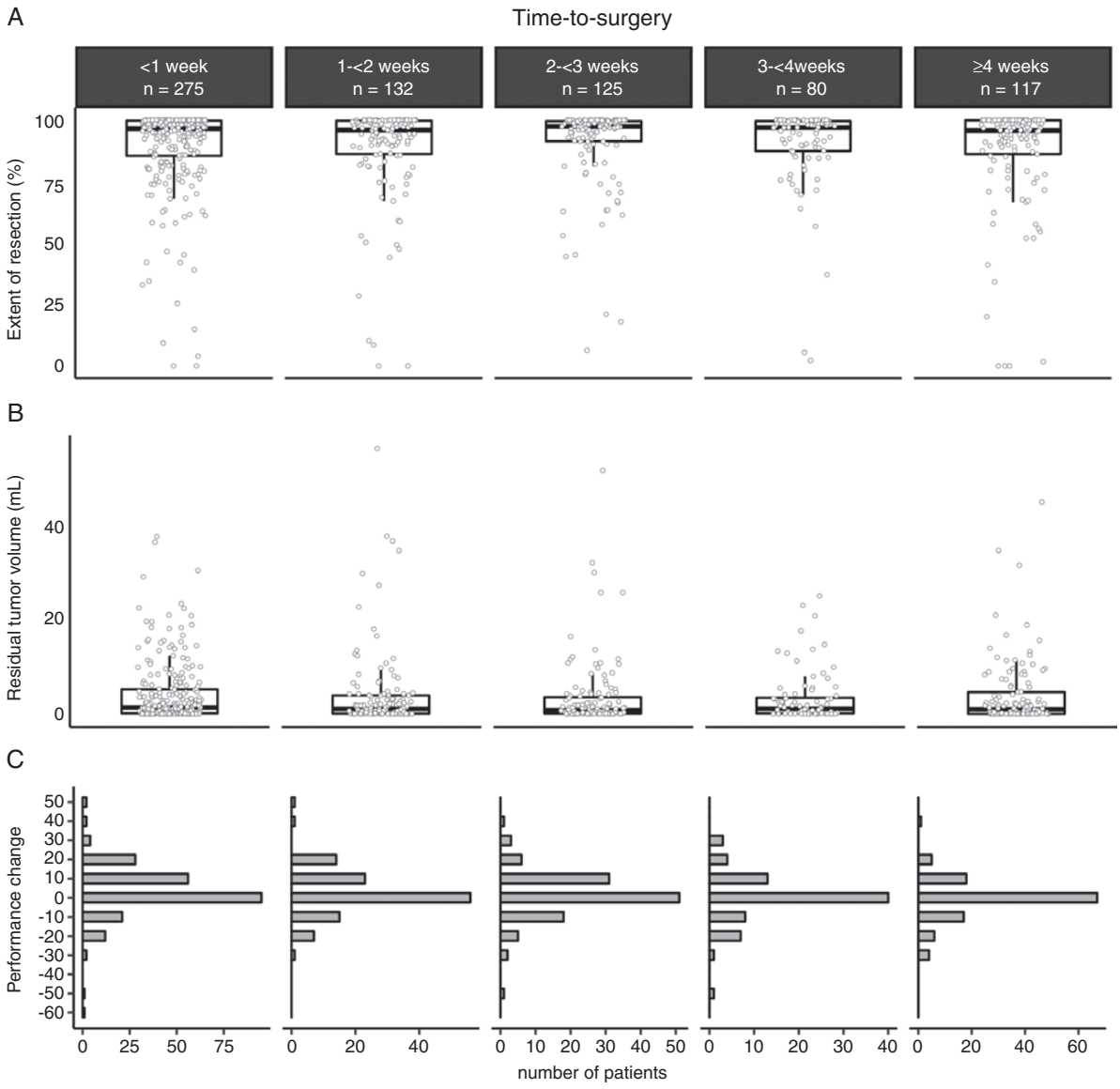

Figure 3. The associations between time-to-surgery in weeks and (A) extent of resection ($P = .16$), (B) residual tumor volume ($P = .69$), and (C) performance change ($P = .34$) in 729 patients with a resection. The distribution median, 25% and 75% quartiles are indicated as hinges, and 1.5 times the interquartile distance as whiskers. Individual patient data is plotted as dots.

Apparently, other factors than tumor location prompt early surgery, such as mass effect, midline shift, or anticipated tumor growth, which were not captured in our analysis.

The literature on the time-to-surgery in patients with glioblastoma is limited. We found 2 studies exploring the impact of route of diagnosis on survival in glioblastoma.[16,17] These studies observed a worse overall survival in patients obtaining a rapid diagnosis by presenting through emergency admission in comparison with routine outpatient services. This may be counterintuitive as patients admitted through emergency departments often have prompt surgery. Worse outcome after urgent surgery has been observed in other malignancies and has been coined the "waiting time paradox."[32] While our patients with a lower performance status and a larger tumor had the shortest time-to-surgery, their performance and survival was comparable to other patients with longer time-to-surgery. Apparently, patients with glioblastoma are not subject to the waiting time paradox, which may be partly explained by the subset of patients rightfully selected for urgent surgery, who are salvaged from poor outcome.

Another study observed a longer survival after shorter time-to-surgery in 63 patients with glioblastoma who present with a seizure as presenting symptom.[15] An explanation for the discrepancy with our results is the difference in median time-to-surgery (13 vs 45 days) and selection bias by presenting symptoms.

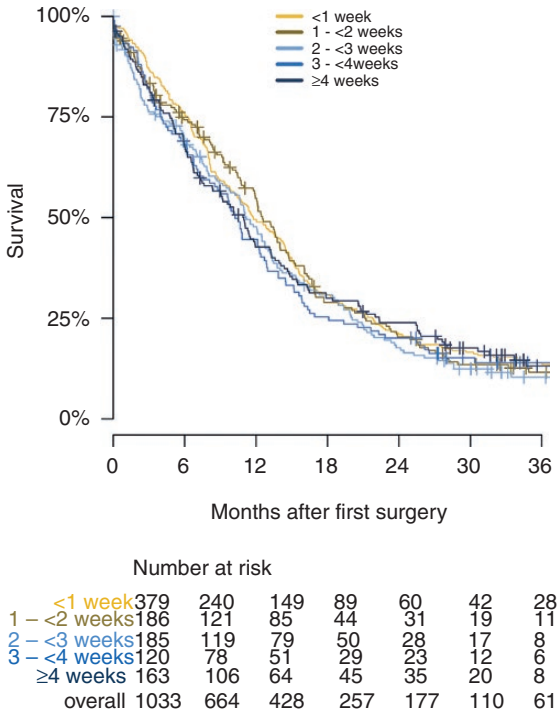

Figure 4. Kaplan–Meier survival plots by time-to-surgery in weeks for all 1033 patients ($P = .84$).

We propose the maximally acceptable time-to-surgery to be at least 1 month, based on several arguments. The observed volumetric doubling time was 22 days in our data, in agreement with others.[10–12] Furthermore, no matter the tumor volume and tumor growth speed, surgery within 1 month does not seem to be related with survival, performance change, or extent of resection. Patients with tumor volumes > 50 mL with more than a month of time-to-surgery appear to have lower extent of resection and shorter survival and could be selected for more urgent surgery. Time-to-surgery within 1 month is feasible, as supported by our data and by another population-based study reporting surgery within 1 month in 86% of 834 patients with glioblastoma, although patient outcome was not analyzed in relation to time-to-surgery in that study.[9] In addition to arguments from patient outcomes, the uncertainty of the diagnosis and prognosis awaiting surgery of a presumably malignant brain tumor can cause great anxiety for newly diagnosed patients, which may be reduced by timely surgery. Nevertheless, our results do not exclude the time to surgery to be acceptable after 1 month in selected patients.

As a reference, a maximally acceptable time-to-surgery has also been reported for other cancer types, for example, 3 months in breast cancer and 5 weeks in colon cancer,[19,33] whereas longer time-to-surgery was associated with shorter survival with median time-to-surgery intervals of 37 days in head-and-neck cancer and 32 days in lung cancer.[21,30] In comparison, the median time-to-surgery of 13 days in our study is much shorter for glioblastoma, possibly due to more rapidly progressive and more alarming neurological symptoms.

Surgery and adjuvant chemoradiotherapy are synergistic treatment modalities for glioblastoma,[34] therefore it is of interest to put time-to-surgery in perspective with time-to-chemoradiotherapy. The optimal time-to-chemoradiotherapy is unclear and practice guidelines vary. One guideline reports that time-to-chemoradiotherapy should not exceed 6 weeks,[5] another reports an optimal time frame of 3–6 weeks,[35] while other reports do not mention timings.[4,6,7] This variation in guidelines is inherent to conflicting results in studies on the time-to-chemoradiotherapy and survival, where some studies report no effect,[9,36] and others report that a shorter or longer[37,38] time-to-chemoradiotherapy is associated with longer survival. Patients with a presumed poorer prognosis receive adjuvant chemoradiotherapy earliest.[39,40] This is in accordance with our findings in time-to-surgery, where patients with low performance status and large tumor volume received surgery the earliest and both are strong negative prognostic factors for survival.

In the last 2 decades, governments have facilitated cancer awareness and fast-track programs to speed up cancer diagnosis and treatment.[41] These programs have been proven effective in reducing referral time and time-to-surgery of cancers such as breast or testicular cancer, however, patients with glioma were the least likely to be referred through fast-track routes.[42] This is due to patients presenting with nonspecific symptoms that are difficult to diagnose in primary care. This underlines the need for timely treatment after radiological diagnosis of glioblastoma, hence initiatives for "fast-track post-radiological-diagnosis" are upcoming.[43] Selection of patients for urgent surgery in these programs is important.

A strong point of this study is the inclusion of unbiased data from multiple centers reflecting clinical practice in support of external validity of our results.

Some limitations are inherent to the data collection of this cohort, in which we were unable to systematically retrieve timings of consultations and tumor board discussions, nor capacity issues on wards and operating rooms. We also have no information on the duration, severity and pace of progression of symptoms before surgery, nor the actual parameters that led to urgent surgery. We had to rely on Karnofsky performance changes which is a rather crude measure of outcome, which may have missed relevant neurological or cognitive decline due to longer time-to-surgery. Additionally, information on quality of life measurements, length of hospital stay, and the need for postoperative rehabilitation was unavailable. Furthermore, we have defined the gadolinium enhancement with enclosed necrosis or cyst as tumor, while this is known to underestimate the extent of glioblastoma infiltration. However, surgical treatment in glioblastoma remains predominantly confined to the contrast-enhanced part.[44] Also, tumor volume segmentation is subject to intra- and interrater agreement variation.[45] Histopathological diagnosis was based on the WHO 2007 criteria for which molecular analysis was not in standard use by most teams at the time, and therefore we were unable to stratify by molecular markers such as IDH1 mutation status and MGMT methylation status. In

addition, other potential prognostic factors were missing, such as time to concurrent chemoradiation. We consider it unlikely that this information would change the absence of an association between time-to-surgery and survival. In practice, this prognostic information only becomes available after decisions on time-to-surgery. Finally, we cannot exclude that longer time to surgery may have led to conversion from planned surgical resection to biopsy due to tumor growth in some patients. This information cannot be reliably retrieved in retrospect.

In conclusion, we found equal extent of resection, residual tumor volume, performance status, and survival following longer times-to-surgery, standing as a testimony to identify patients for urgent surgery. Typically, these are patients with lower performance status and larger tumor volume. We postulate that glioblastoma surgery should not be delayed by more than 1 month from the initial diagnostic scan.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

glioblastoma | neurosurgical procedures | time-to-treatment | treatment outcome | waiting list

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Conflicts of interest statement. Brainlab generously provided segmentation software as a contribution in kind to this study. The authors declare that they have no competing interests.

Authorship Statement. Concept and design: D.M.J.M., P.A.J.T.R., W.P.V., F.B., and P.C.W.H. Acquisition and interpretation of data: D.M.J.M., P.A.J.T.R., R.S.E., M.G.W., M.V., and P.C.D.W. Statistical analyses: D.M.J.M. Preparation of figures and tables: D.M.J.M. and P.C.W.H. Manuscript preparation, including revision stages: all authors. All authors have read and approved the final version of the manuscript.

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