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Between-hospital variation in time to glioblastoma surgery: a report from the Quality Registry Neuro Surgery in the Netherlands

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OBJECTIVE Patients with glioblastoma are often scheduled for urgent elective surgery. Currently, the impact of the waiting period until glioblastoma surgery is undetermined. In this national quality registry study, the authors determined the wait times until surgery for patients with glioblastoma, the risk factors associated with wait times, and the risk-standardized variation in time to surgery between Dutch hospitals. The associations between time to surgery and patient outcomes were also explored.

METHODS Data from all 4589 patients who underwent first-time glioblastoma surgery between 2014 and 2019 in the Netherlands were collected by 13 hospitals in the Quality Registry Neuro Surgery. Time to surgery comprised 1) the time from first MR scan to surgery (MTS), and 2) the time from first neurosurgical consultation to surgery (CTS). Long MTS was defined as more than 21 days and long CTS as more than 14 days. Potential risk factors were analyzed in multivariable logistic regression models. The standardized rate of long time to surgery was analyzed using funnel plots. Patient outcomes including Karnofsky Performance Scale (KPS) score change, complications, and survival were analyzed by multivariable logistic regression and proportional hazards models.

RESULTS The median overall MTS and CTS were 18 and 9 days, respectively. Overall, 2576 patients (56%) had an MTS within 3 weeks and 3069 (67%) had a CTS within 2 weeks. Long MTS was significantly associated with older age, higher preoperative KPS score, higher American Society of Anesthesiologists comorbidity class, season, lower hospital case volume, university affiliation, and resection. Long CTS was significantly associated with higher baseline KPS score, university affiliation, resection, more recent year of treatment, and season. In funnel plots, considerable practice variation was observed between hospitals in patients with long times to surgery. Fewer patients with KPS score improvement

ABBREVIATIONS AIC = Akaike Information Criterion; ASA = American Society of Anesthesiologists; CI = confidence interval; CTS = time from first neurosurgical consultation to surgery; HR = hazard ratio; KPS = Karnofsky Performance Scale; MTC = time from first MR scan to consultation; MTS = time from first MR scan to surgery; OR = odds ratio; QRNS = Quality Registry Neuro Surgery.

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were observed after a long time until resection. Long CTS was associated with longer survival. Complications and KPS score decline were not associated with time to surgery.

CONCLUSIONS Considerable between-hospital variation among Dutch hospitals was observed in the time to glioblastoma surgery. A long time to resection impeded KPS score improvement, and therefore, patients who may improve should be identified for more urgent resection. Longer survival was observed in patients selected for longer time until surgery after neurosurgical consultation (CTS).

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KEYWORDS waiting time; diagnostic delay; referral; glioblastoma; oncology

Patients with suspected glioblastoma are often scheduled for urgent elective surgery. The wait time until glioblastoma surgery could play a role in patient outcome, as associations between preoperative tumor volumes and extent of resection, and between extent of resection and survival, have been demonstrated in these patients.[1,2] The average duration until glioblastoma tissue volume doubles is approximately 1 month, thus it is conceivable that tumor growth with progressive brain infiltration may impede functional outcome and survival.[1,3]

In international guidelines for neuro-oncology, acceptable timing for glioblastoma surgery has not yet been specified.[4–6] Consequently, surgical wait times varied widely in population-based studies evaluating the patterns of glioblastoma care, i.e., 27%–86% of patients had surgery within 1 month.[7–10] Evidence for the impact of wait time on patient outcome in neuro-oncological care is sparse and inconclusive. One study found that time to surgery longer than 45 days in patients with glioblastoma who presented with only a seizure was associated with decreased survival.[11] Another study demonstrated that patients admitted through emergency services with a median of 8 days until surgery had a significantly shorter survival than patients presenting through outpatient consultation with a median of 26 days until surgery.[12] In a recent study, time to surgery was not associated with survival.[10] In other cancer types, such as breast and colon cancer, increased wait time to surgical intervention was associated with shorter survival, hence minimal preoperative delay was advised.[13,14] Insight into the impact of wait time to glioblastoma surgery on patient outcome should enable better management decisions and thus fuel discussions on practice guidelines.

In this study, we determined the time until surgery for patients with glioblastoma in a prospective national quality registry, the risk factors associated with long wait times, and the risk-standardized variation in time to surgery between hospitals in the Netherlands. We also aimed to evaluate the association between time to surgery and Karnofsky Performance Scale (KPS) score change, complication rate, and survival.

Methods

A nationwide population-based study was performed in the Netherlands. Data were retrieved from the Quality Registry Neuro Surgery (QRNS), a nationwide registry from the Dutch Society for Neurosurgery, in which all Dutch institutions with neurosurgical units are obliged to register patients with glioblastoma.[15,16] Patient data were prospectively recorded in the QRNS by neurosurgeons, nurse specialists in neuro-oncology, and trained physician assistants. In previous studies, between-hospital variation in complications, decline in patient performance after surgery, and survival have been reported from this registry.[17,18] Data were obtained and de-identified by the trusted third party Stichting Informatievoorziening Zorg, a national institute concerned with the registration and data handling of health care institutes in the Netherlands. Ethical approval was waived to perform this study and individual written informed consent was not needed because the study was not subject to the Medical Research Involving Human Subjects Act.[19] A de-identified data set was obtained from the trusted third party for analysis.

Patients

All patients who underwent first-time glioblastoma surgery in the Netherlands between January 2014 and December 2019 were studied. Data were collected for patients 18 years of age or older at surgery with histologically confirmed glioblastoma, according to the 2007 *WHO Classification of Tumours of the Central Nervous System*[32] (until 2015) and the 2016 WHO classification[33] thereafter. Patients underwent treatment at one of 13 neurosurgical centers providing neuro-oncological care: Amsterdam University Medical Centers, Erasmus University Medical Center, Isala Hospital, Haaglanden Medical Center/Leiden University Medical Center, Maastricht University Medical Center, Martini Hospital, Medical Center Slotervaart, Medical Center Twente, Northwest Clinics, Radboud University Medical Center, Elisabeth-Tweesteden Hospital, University Medical Center Utrecht, and University Medical Center Groningen.

Patient characteristics included age at diagnosis, sex, the last KPS score before surgery and 6–8 weeks after surgery, and American Society of Anesthesiologists (ASA) classification. Treatment characteristics included dates of first MR scan, first neurosurgical consultation and surgery, year and season of treatment, and type of surgery (biopsy or resection). Biopsy was defined as surgical removal of tissue for diagnosis only, either by open or needle biopsy. Hospital characteristics included the average case volume per year, university affiliation, and the rate of biopsy surgery over the observation period.

Outcome Measures

The main outcome measures were times to surgery, comprising 1) the time from first MR scan to surgery (MTS), 2) the time from first neurosurgical consultation to surgery (CTS), and 3) the time from first MR scan to consultation (MTC). The first MR scan was typically requested by a neurologist before referral to a neurosurgeon for first neurosurgical consultation. Long MTS was defined as more than 21 days from the first MR scan, and

long CTS was defined as more than 14 days from the first neurosurgical consultation, based on the quality standards of the Dutch Society for Neurosurgery.[20]

The secondary outcome measures were complications, performance alterations after surgery, and survival. Complications were graded by the revised Clavien-Dindo classification.[21] This classification ranks complications based on the therapy used to treat the complication. A complication was defined as Clavien-Dindo classification of grade II and higher. Performance alterations were calculated by subtracting the baseline KPS score prior to surgery from the KPS score at 6–8 weeks after surgery. A performance decline was defined as a negative performance change of more than 10 points, and a performance improvement was defined as a positive performance change of more than 10 points. Performance improvement was analyzed on the subset of patients amenable to improvement, i.e., those with a preoperative KPS score of 80 or lower. Survival was analyzed in days between surgery and death of any cause, with censoring at the last date of follow-up or the lookup date of alive status.

Statistical Analysis

Distributions of times to surgery were first plotted in histograms. Differences in times to surgery between type of surgery were compared with Wilcoxon rank-sum tests, and the correlation as product-moment coefficient. Patient- and treatment-related variables, including age in years, sex, ASA classification, preoperative KPS score, year of treatment, and type of surgery, were subsequently assessed as case-mix correction factors in multivariable logistic regression models with long time to surgery as the dependent variable. The models with the lowest Akaike Information Criterion (AIC) were selected as a trade-off between goodness of fit and model simplicity and were used to determine the probability of long wait time to surgery per patient. The expected risk of long time to surgery was calculated for each patient based on the statistically significant risk factors. Variation in risk-standardized rate of long time to surgery was compared between hospitals by plotting the expected number of events (based on a hospital's patient population) versus the ratio of observed and expected events, using funnel plots. Rates of hospitals outside the 95% confidence intervals (CIs) were considered to indicate statistically significant deviations from expected rates. The associations between times to surgery and complications and KPS score alterations were analyzed using chi-square tests and multivariable logistic regression models. Overall survival was evaluated by Kaplan-Meier curves and in multivariable proportional hazard models. The associations between times to surgery and patient outcomes were assessed separately for resections and biopsies. Analyses were based on complete cases regarding information on covariates. A p value < 0.05 was considered statistically significant. Statistical analyses were performed in R (version 4.1.0; R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, 2017).

Results

Of the 4589 patients included, the MTS was available for 4131 patients (90%) and the CTS for 4227 patients (92%). Patient characteristics per hospital are listed in Table 1.

Time to Surgery

The overall distributions of MTS, CTS, and MTC are plotted in Fig. 1A–C, respectively, and in a stacked line plot per patient in Fig. 1D. The overall median MTS was 18 days, ranging from a median of 11 to 24 days between hospitals. The median MTS was 18 days for resections and 17 days for biopsies (not a significant difference). The MTS was within 21 days in 2576 (56%) patients, ranging from 32% to 81% between hospitals. The overall median CTS was 9 days, ranging from a median of 6 to 13 days between hospitals. The median CTS was 10 days for resections and 8 days for biopsies ($p < 0.0001$). The CTS was within 14 days in 3069 (67%) patients, ranging from 49% to 90% between hospitals. The overall median MTC was 7 days, ranging from a median of 6 to 11 days between hospitals. Negative times reflect the few urgent cases with immediate hospital transfer and emergency surgery for instances of hemorrhage or hydrocephalus from a tumor based on CT scans, for whom neurosurgical consultation and MRI followed surgery. The correlation between MTS and CTS, as plotted in Fig. 1E, was moderate ($r = 0.41$, 95% CI 0.38–0.44).

Risk Factors for Long Wait Times to Surgery

A higher risk for long MTS was associated with older age (odds ratio [OR] 1.003, 95% CI 1.001–1.004), higher preoperative KPS score (OR 1.007, 95% CI 1.006–1.008), higher ASA class (II vs I: OR 1.043, 95% CI 1.003–1.083; III vs I: OR 1.093, 95% CI 1.038–1.150), the season (summer vs fall: OR 1.067, 95% CI 1.023–1.112), lower hospital case volume (OR 0.999, 95% CI 0.999–1.000), university affiliation (OR 1.220, 95% CI 1.172–1.270), and lower biopsy rate (OR 0.813, 95% CI 0.681–0.971). This multivariable model had an AIC of 5286 and the interaction terms were not significantly associated. A higher risk for long CTS was associated with higher baseline KPS score (OR 1.004, 95% CI 1.003–1.005), resection compared to biopsy (OR 0.921, 95% CI 0.895–0.948), more recent year of treatment (2018 vs 2014: OR 1.099, 95% CI 1.050–1.149; 2019 vs 2014: OR 1.124, 95% CI 1.074–1.175), the season (spring vs fall: OR 1.071, 95% CI 1.031–1.112; summer vs fall: OR 1.057, 95% CI 1.018–1.097; winter vs fall: OR 1.039, 95% CI 1.001–1.079) and university affiliation (OR 1.231, 95% CI 1.189–1.275). This multivariable model had an AIC of 4721 and none of the interaction terms were statistically significant.

Risk-Standardized Variation in Long Wait Times Until Surgery Between Hospitals

Funnel plots were constructed with sums of expected numbers of patients with long times to surgery per hospital versus the ratio of observed and expected numbers of patients with long times to surgery per hospital, as shown in Fig. 2A for MTS and in Fig. 2B for CTS. One hospital had more patients with long MTS than expected (Fig. 2A, hospital d), and 2 hospitals had fewer patients than expected (Fig. 2A, hospitals e and l). Five hospitals had more

TABLE 1. Patient characteristics per hospital and overall

Variable	Hospital													Overall
	a	b	c	d	e	f	g	h	i	j	k	l	m	
No. of patients	603	594	580	568	541	328	299	290	236	171	161	110	108	4589
No. of females (%)	213 (35.3)	232 (39.1)	207 (35.7)	193 (34.0)	148 (27.4)	131 (39.9)	103 (34.4)	115 (39.7)	88 (37.3)	68 (39.8)	66 (41.0)	32 (29.1)	45 (41.7)	1641 (35.8)
Mean age (SD), yrs	62.4 (11.9)	63.5 (11.4)	57.3 (13.2)	60.2 (11.8)	62.3 (10.7)	62.3 (12.1)	61.0 (11.9)	60.3 (12.8)	61.9 (11.7)	60.6 (12.1)	62.0 (11.6)	62.8 (11.2)	61.4 (11.0)	61.3 (12.0)
ASA class														
I	112	53	161	140	172	71	48	58	38	45	14	34	20	966
II	364	424	320	279	281	201	196	171	143	96	114	50	61	2700
III	115	108	91	122	68	45	46	38	48	24	28	20	26	779
IV	12	6	0	5	3	2	3	1	4	2	3	2	1	44
V	0	3	6	0	1	0	0	0	2	1	0	0	0	13
Missing	0	0	2	18	15	8	6	9	1	2	2	4	0	67
KPS score														
100	19	52	128	81	37	14	21	37	25	34	22	9	4	483
90	141	208	179	140	297	131	83	94	79	79	53	46	26	1556
80	173	181	122	145	104	84	72	53	47	32	25	20	20	1078
70	136	82	77	103	27	18	34	54	36	14	22	7	27	637
60	80	49	43	51	11	41	43	10	22	5	18	4	21	398
50	30	17	22	16	13	14	36	2	23	5	11	4	9	202
40	11	2	2	5	1	3	4	1	2	0	5	3	1	40
30	6	1	3	2	2	1	2	1	0	0	3	1	0	22
20	3	1	1	3	1	3	4	1	1	2	1	2	0	23
10	1	1	1	2	0	0	0	0	0	0	0	0	0	5
Missing	3	0	2	20	48	19	0	37	1	0	1	14	0	145
Year														
2014	90	80	87	75	88	49	46	47	47	15	20	16	25	685
2015	100	81	70	90	80	56	45	38	35	18	26	12	22	673
2016	94	87	92	91	100	36	50	38	33	28	28	28	22	727
2017	108	101	123	114	72	59	47	43	43	33	21	8	20	792
2018	110	118	101	106	88	62	52	58	48	36	36	8	19	842
2019	101	127	107	92	113	66	59	66	30	41	30	38	0	870
University hospital	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No	7
Biopsy, n (%)	183 (30.3)	167 (28.1)	133 (22.9)	130 (22.9)	222 (41.0)	75 (22.9)	82 (27.4)	160 (55.2)	79 (33.5)	60 (35.1)	50 (31.1)	37 (33.6)	29 (26.9)	1407 (30.7)
Median MTS (IQR), days	19 (14)	16 (13)	24 (21)	19 (14)	17 (9)	11 (12)	21 (15)	18 (18)	20 (16)	18 (12)	16 (11)	14 (9)	16 (15.5)	18 (16)
25th–75th percentile	12–26	10–23	15–36	14–28	13–22	7–19	14–29	12–30	13–29	12–24	11–22	10–19	9.5–25	11–27
Missing, n (%)	0 (0)	7 (1.2)	85 (14.7)	18 (3.2)	306 (56.6)	8 (2.4)	0 (0)	5 (1.7)	1 (0.4)	8 (4.7)	0 (0)	3 (2.7)	17 (15.7)	458 (10.0)
MTS ≤21 days, n (%)	360 (59.7)	420 (70.7)	204 (35.2)	327 (57.6)	171 (31.6)	267 (81.4)	152 (50.8)	172 (59.3)	130 (55.1)	107 (62.6)	119 (73.9)	86 (78.2)	61 (56.5)	2576 (56.1)

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TABLE 1. Patient characteristics per hospital and overall

Variable	Hospital													Overall
	a	b	c	d	e	f	g	h	i	j	k	l	m	
Median MTC (IQR), days	6 (9)	8 (9)	10 (13)	7 (8)	8 (9)	6 (11)	11 (10)	6 (9.3)	8 (10)	8 (8.3)	7 (7)	8 (7.8)	8 (11.5)	7 (10)
25th–75th percentile	2–11	4–13	5–18	4–12	5–14	1–12	6–16	2–11.3	4–14	4.8–13	3–10	4.3–12	3.8–15.3	3–13
Missing, n (%)	4 (0.7)	11 (1.9)	91 (15.7)	25 (4.4)	309 (57.1)	11 (3.4)	1 (0.3)	10 (3.4)	6 (2.5)	11 (6.4)	0 (0)	8 (7.3)	20 (18.5)	507 (11)
Median CTS (IQR), days	10 (11)	7 (8)	12 (13)	12 (10)	7 (6)	6 (6)	10 (11)	13 (14)	12 (10)	9 (7)	8 (9)	6 (6)	6 (9)	9 (10)
25th–75th percentile	6–17	4–12	6–19	7–17	4–10	2–8	4–15	7–21	6–16	6–13	5–14	4–10	1–10	5–15
Missing, n (%)	4 (0.7)	4 (0.7)	66 (11.4)	10 (1.8)	236 (43.6)	5 (1.5)	1 (0.3)	10 (3.4)	6 (2.5)	7 (4.1)	0 (0)	6 (5.5)	6 (5.6)	361 (7.9)
CTS ≤14 days, n (%)	389 (64.5)	484 (81.5)	305 (52.6)	348 (61.3)	266 (49.2)	297 (90.5)	219 (73.2)	156 (53.8)	155 (65.7)	134 (78.4)	127 (78.9)	99 (90.0)	90 (83.3)	3069 (66.9)
Patients w/ a complication, n (%)	73 (12.1)	61 (10.3)	40 (6.9)	81 (14.3)	48 (8.9)	24 (7.3)	47 (15.7)	1 (0.3)	14 (5.9)	5 (2.9)	20 (12.4)	4 (3.6)	9 (8.3)	427 (9.3)
Patients w/ performance improvement, n (%)	31 (5.1)	43 (7.2)	53 (9.1)	48 (8.5)	10 (1.8)	15 (4.6)	31 (10.4)	15 (5.2)	11 (4.7)	7 (4.1)	19 (11.8)	5 (4.5)	25 (23.1)	313 (6.8)
Patients w/ performance decline, n (%)	123 (20.4)	184 (31.0)	101 (17.4)	115 (20.2)	74 (13.7)	43 (13.1)	66 (22.1)	19 (6.6)	80 (33.9)	52 (30.4)	38 (23.6)	19 (17.3)	6 (5.6)	920 (20.0)
Median survival, mos	10.3	10.7	12.1	9.9	9.8	9.4	10.1	9.4	9.3	9.5	9.7	9.6	10.9	10.3

patients with long CTS than expected (Fig. 2B, hospitals a, c, d, h, and k), and 3 hospitals had fewer (Fig. 2B, hospitals b, e, and l). A difference was observed between university hospitals compared to general hospitals, indicating shorter times to surgery in the latter.

Association Between Time to Surgery and Complications

Overall, a complication occurred in 427 patients (9.3%). The complication grades did not significantly differ between timely and long MTS for patients who had a biopsy or resection ($p = 0.943$ and 0.576, respectively; Fig. 3A). Likewise, the complication grades did not significantly differ between timely and long CTS for patients who had a biopsy or a resection ($p = 0.665$ and 0.999, respectively; Fig. 3B). A higher probability of a complication was associated with higher ASA class (II vs I: OR 1.55, 95% CI 1.13–2.17; III vs I: OR 1.97, 95% CI 1.35–2.90; IV vs I: OR 2.45, 95% CI 0.97–5.59), lower baseline KPS score (OR 0.98, 95% CI 0.97–0.98), and resection versus biopsy (OR 2.65, 95% CI 1.99–3.58). Neither the MTS (OR 1.01, 95% CI 0.80–1.27) nor the CTS (OR 1.08, 95% CI 0.847–1.37) was associated with complications. This multivariable model had an AIC of 2568 and none of the interaction terms were statistically significant.

Association Between Time to Surgery and KPS Score Change

The KPS score changes did not differ between timely and long MTS in patients who underwent a biopsy (Fig. 3C, $p = 0.465$). In contrast, KPS score changes differed significantly between patients who had a resection within 21 days and those later than 21 days (Fig. 3C, $p = 0.0005$); fewer KPS score improvements were observed after long MTS. No difference was observed in KPS score changes between timely and long CTS in patients with biopsy (Fig. 3D, $p = 0.566$), but a significantly different KPS score change was observed between patients who had a resection within 14 days compared with those later than 14 days ($p = 0.0005$). Line plots of KPS score change per patient are shown in Fig. 3E in relation to MTS and in Fig. 3F in relation to CTS. It is evident that patients with a preoperative KPS score of 90 or 100 have no margin of improvement and hence were excluded from analysis of KPS score change. These figures indicate that improvement was observed from all levels of preoperative KPS score after timely surgery, and less improvement from all levels of preoperative KPS score after long times to surgery.

Overall, a performance improvement was observed in 313 (12%) of the 2550 patients who could potentially improve (baseline KPS score ≤ 80). A higher probability of performance improvement was associated with lower age (OR 0.973, 95% CI 0.962–0.985), lower ASA class (IV vs I: OR 0.269, 95% CI 0.069–0.873), lower baseline KPS score (OR 0.928, 95% CI 0.917–0.939), resection versus biopsy (OR 8.64, 95% CI 5.63–13.8), and either timely MTS (OR 1.47, 95% CI 1.06–2.05) or timely CTS (OR 1.52, 95% CI 1.07–2.17). Apparently, the odds for KPS score improvement increased the most for younger patients with a lower KPS score, when the tumor was resected within 21 days from the first MR scan, or within 14

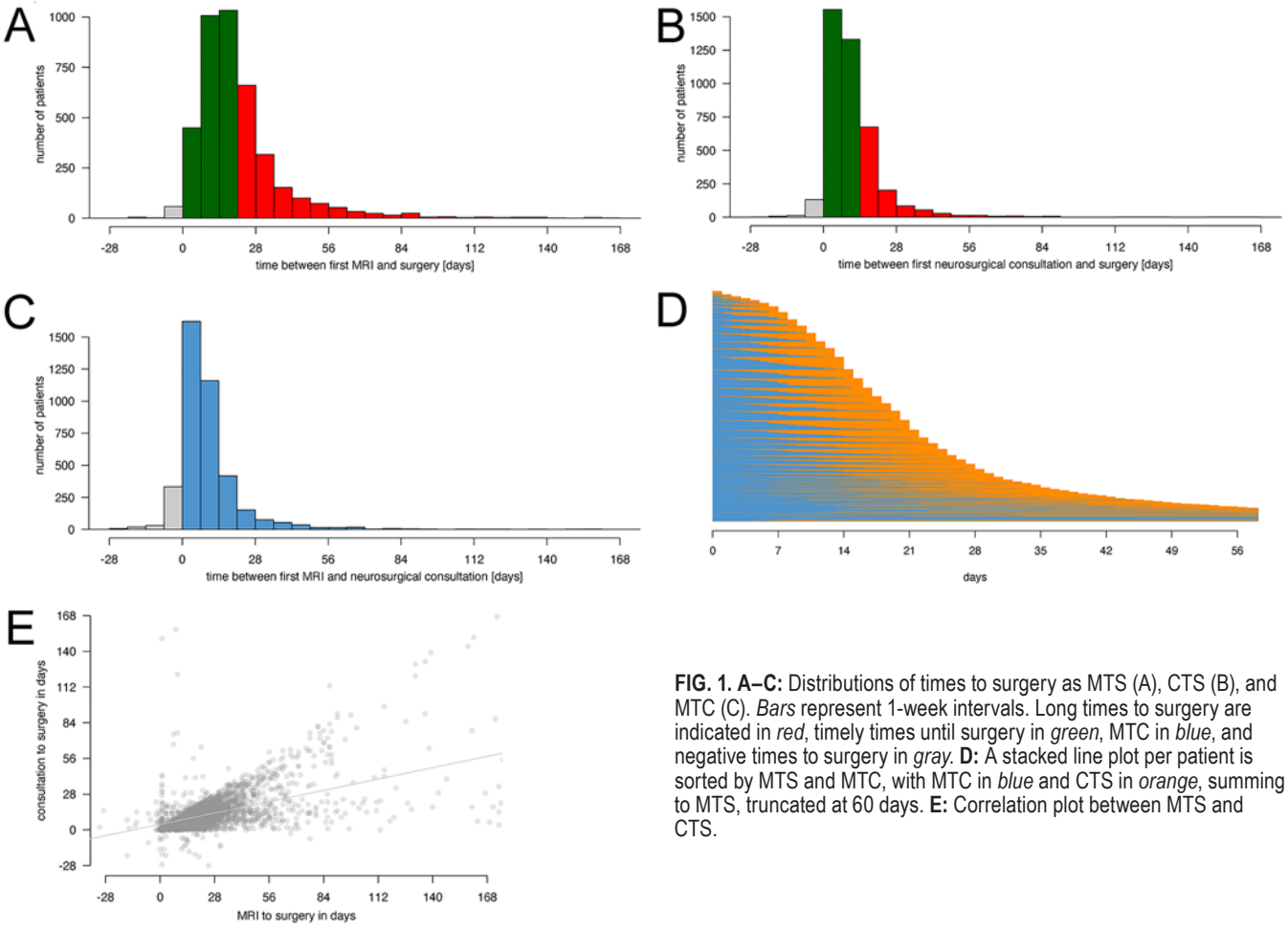

FIG. 1. A–C: Distributions of times to surgery as MTS (A), CTS (B), and MTC (C). *Bars* represent 1-week intervals. Long times to surgery are indicated in *red*, timely times until surgery in *green*, MTC in *blue*, and negative times to surgery in *gray*. **D:** A stacked line plot per patient is sorted by MTS and MTC, with MTC in *blue* and CTS in *orange*, summing to MTS, truncated at 60 days. **E:** Correlation plot between MTS and CTS.

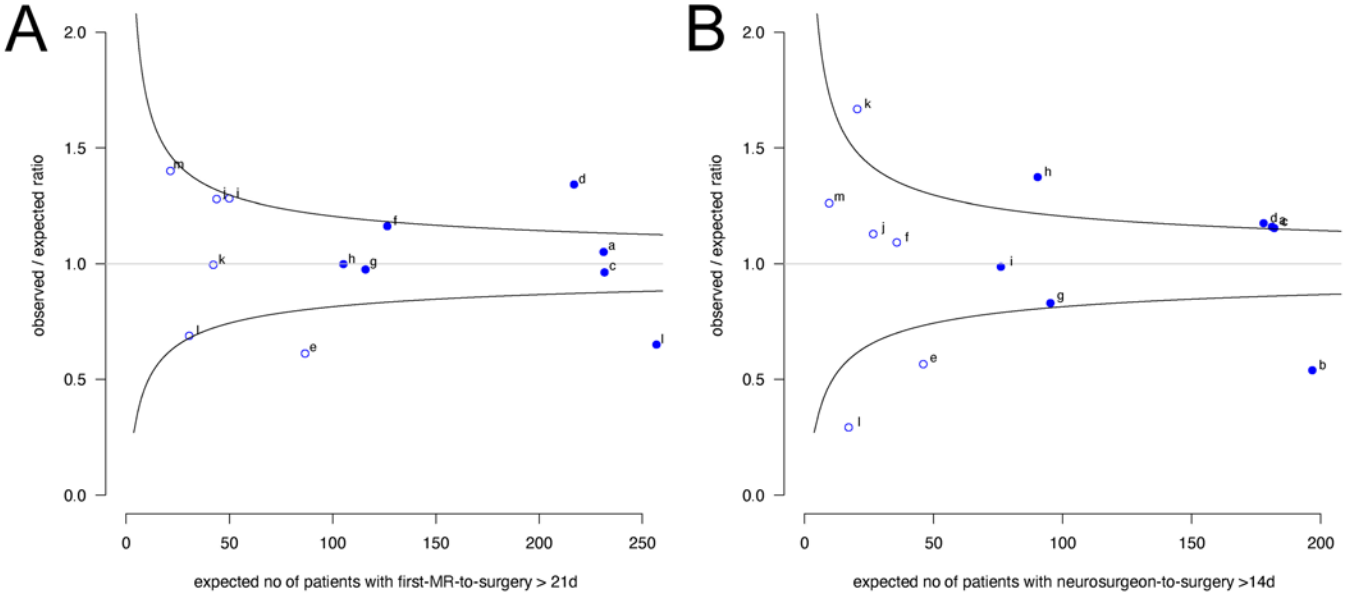

FIG. 2. Funnel plots of long times to surgery as MTS (**A**) and CTS (**B**). *Dots* represent hospitals with *letters* corresponding to identifications in Table 1. *Open dots* indicate general hospitals and *filled dots* university hospitals. The 95% CIs are represented by the funnels. Hospitals above the upper funnel have significantly more patients with a long time to surgery than expected, and those below the lower funnel have significantly fewer patients than expected.

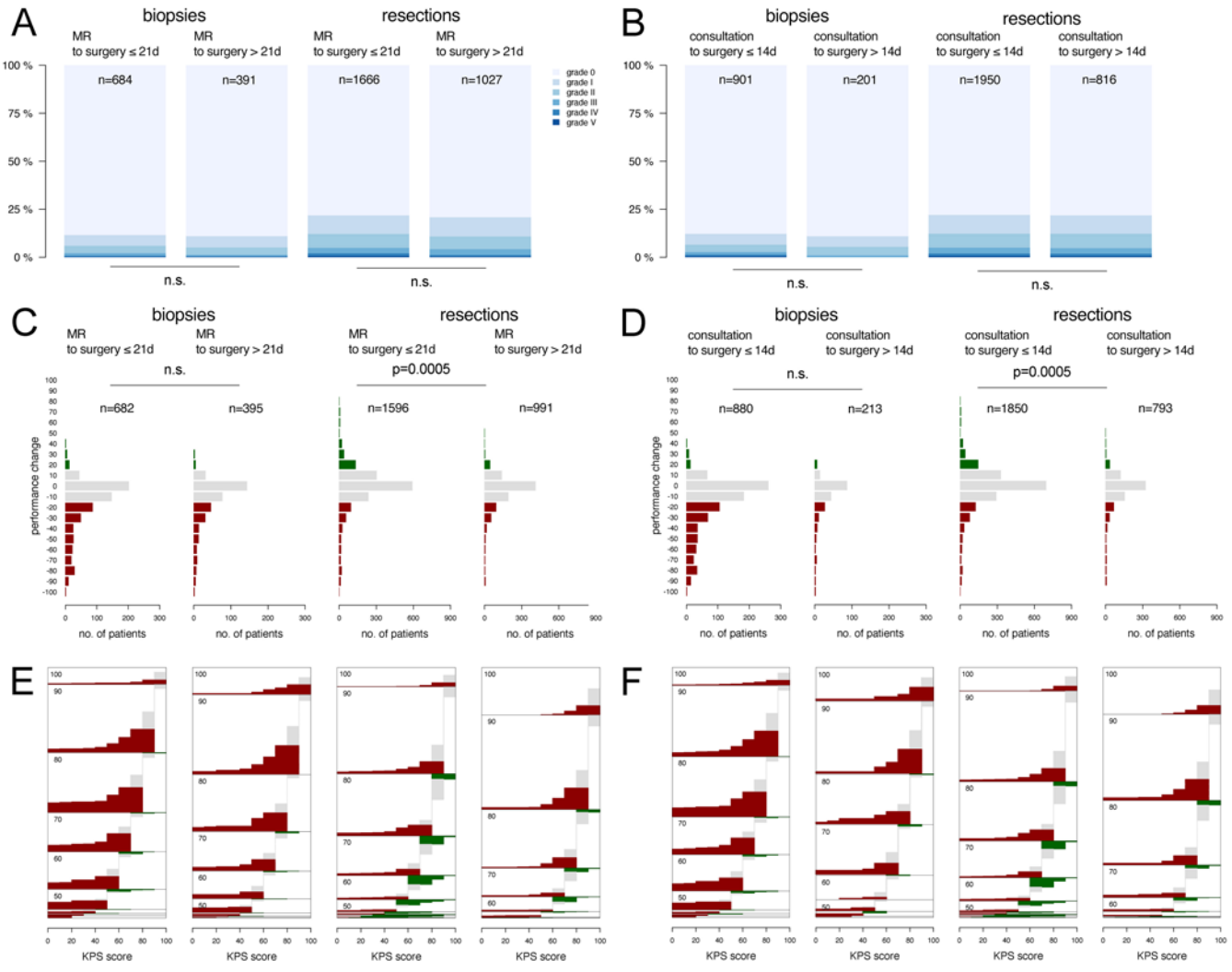

FIG. 3. A–D: Complications (A and B) and KPS score changes (C and D) stratified by long time to surgery for biopsies and resections for MTS (A and C, ≥ or < 21 days) and CTS (B and D, ≥ or < 14 days). Complications are graded according to the Clavien-Dindo classification as delineated in the key. *Green* KPS score changes indicate improvement, *red* KPS score changes indicate decline. **E and F:** Line plots of KPS score changes per patient are sorted by baseline KPS score and change. The panels E and F follow the subgroups indicated in C and D. Each *horizontal line* represents 1 patient. *Boxes* indicate the baseline KPS score categories as listed on the left side in each graph. Score improvement is plotted in *green*, unchanged performance in *gray*, and decline in *red*. n.s. = not significant.

days from neurosurgical consultation. The multivariable model including MTS was the most robust with an AIC of 1341 without significant interaction terms.

Overall, a performance decline was observed in 920 (20%) of all 4589 patients potentially prone to decline. A higher risk of performance decline was associated with older age (OR 1.02, 95% CI 1.01–1.03), higher ASA class (II vs I: OR 1.26, 95% CI 1.02–1.57; III vs I: OR 1.66, 95% CI 1.27–2.17), and biopsy versus resection (OR 2.56, 95% CI 2.18–3.00). Neither the MTS (OR 1.02, 95% CI 0.861–1.20) nor the CTS (OR 0.940, 95% CI 0.781–1.13) was associated with performance decline. The multivariable model had an AIC of 4036 without significant interaction terms.

Association Between Time to Surgery and Survival

The median overall patient survival was 10.3 months. Survival was plotted for MTS subgroups in week intervals (Fig. 4A). Longer survival was observed for patients with MTS within a week (median survival 13.3 months) and longer than 4 weeks (median survival 11.8 months; $p = 0.0002$, log-rank test). Survival for CTS subgroups (in weeks) demonstrated longer survival for patients operated at longer-week intervals (Fig. 4B; $p < 0.0001$, log-rank test). In a multivariable model, shorter survival was associated with older age (hazard ratio [HR] for death 1.03, 95% CI 1.02–1.03), lower preoperative KPS score (HR 0.98, 95% CI 0.98–0.98), more recent years of treatment (2017 vs 2014: HR 1.26, 95% CI 1.12–1.42; 2018 vs 2014: HR 1.37, 95% CI 1.20–1.53; 2019 vs 2014: HR 1.43, 95% CI 1.23–1.66), and biopsy compared to resection (HR 2.27, 95% CI 2.10–2.45). In this multivariable model, CTS as a binary variable was associated with survival (HR 0.90, 95% CI

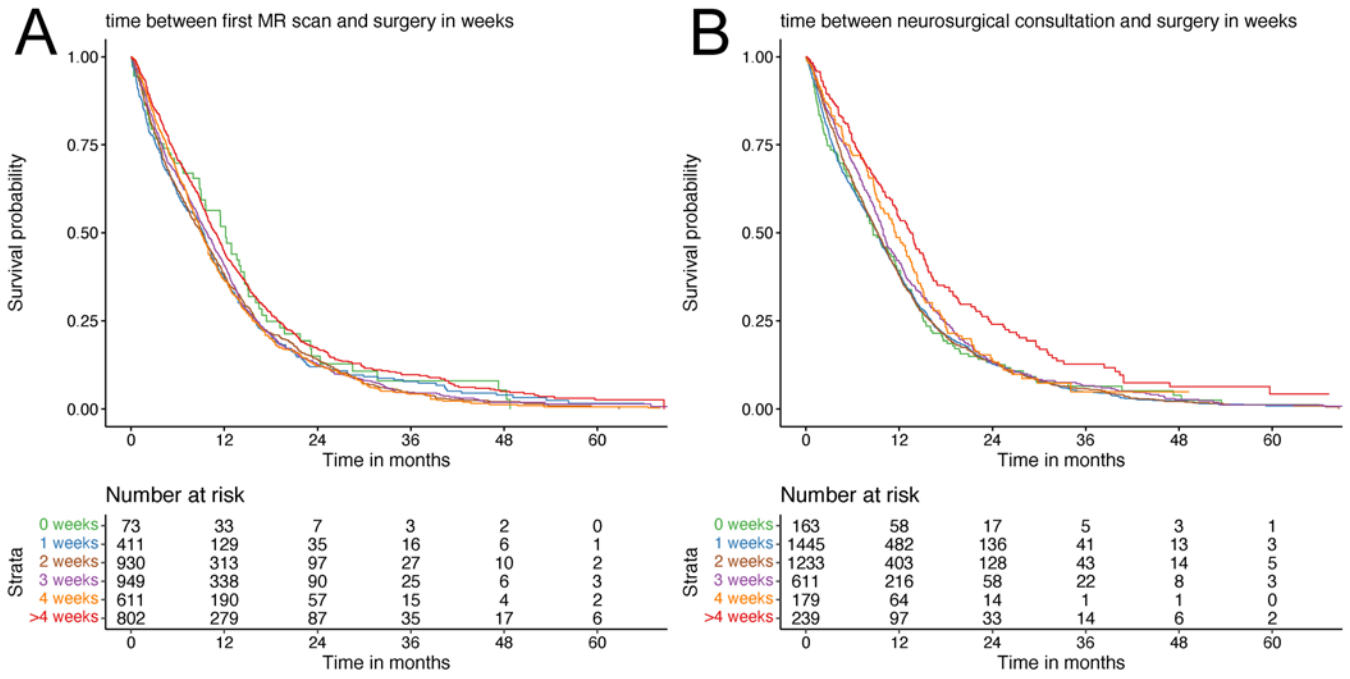

FIG. 4. Kaplan-Meier plots of overall survival stratified by weeks to surgery for MTS (**A**) and CTS (**B**). Number of patients at risk per stratum are tabulated.

0.83–0.98), indicating longer survival was associated with longer time to surgery after neurosurgical consultation. In contrast, MTS as a binary variable (HR 0.94, 95% CI 0.87–1.02) or as measurement in days (HR 1.00, 95% CI 0.99–1.00), or CTS as measurement in days (HR 1.00, 95% CI 0.99–1.00), were not associated with survival.

Discussion

The main findings of this study are: 1) the national quality standards of wait times to surgery are met in 67% of all patients with a considerable practice variation between hospitals; 2) patients with longer wait times until surgery are characterized by a higher KPS score, resection, season, more recent year of treatment, and treatment in a university-affiliated hospital, and possibly by older age, higher ASA class, and treatment in a hospital with lower case volume or higher rate of biopsy surgery; and 3) fewer KPS score improvements are observed in patients with longer times to resection, while complications are not associated with time to surgery, and longer survival is observed in patients selected for longer time to surgery after neurosurgical consultation.

Several factors may affect the times until surgery as the time between first symptoms and surgical treatment can be broken down along the care chain. In the Netherlands, a patient with neurological symptoms is typically referred by a general practitioner to the outpatient clinic for a neurologist in a nearby general hospital or presents to an emergency department directly. A neurologist then assesses the patient's condition and orders brain imaging. If the patient is at the emergency department, a prompt CT scan is usually performed first, and after hospital admission an urgent MR scan follows the same day. In cases of referral to a neurologist as an outpatient, an initial MR scan within a few days is typically performed.[22] Once a brain tumor is suspected based on the images, the patient is referred to an oncological neurologist or neurosurgeon of a specialized multidisciplinary neuro-oncological team for consultation, often in another hospital.[22] Referral as outpatient or clinical admission transfer depends on the patient's condition and the radiological findings. The patient is scheduled for surgery as deemed suitable, depending on the anticipated urgency based on symptom progression, steroid dependency, tumor size and mass effect, and expected histopathology, as well as resource constraints. Limited resources may comprise hospital admission capacity, availability on the surgical schedule, and personnel on the ward, operating room, and postoperative care unit.[10,13] Furthermore, preoperative anesthetic assessment is required before surgical approval, possibly with additional diagnostics and optimization of comorbidities.[23] An unexpected finding in our study was that time to surgery depended on the season. Perhaps this can be explained by patient reluctance to seek medical attention or reduced hospital activity during holidays, or by seasonal variation in glioblastoma incidence. At any of these stages along the neuro-oncological care chain, potential delays in time to surgery can arise. Furthermore, differing healthcare infrastructures between countries may affect time to surgery, such as with initial presentation to a general practitioner, an emergency department, or a neuro-oncological specialist. As an example, patients with a new diagnosis of any intracranial pathology in the US are typically referred to the emergency department, in Australia directly to a neurosurgeon often within 24 hours,[11,24,25] while patients in the United Kingdom and France have a similar referral

route as in the Netherlands. Therefore, we distinguished between time from first MR scan and time from first neurosurgical consultation in this study population. The narrower distribution of CTS compared to MTS clearly indicates that timing varies more before neurosurgical consultation than after. Notably, longer survival was associated with longer CTS but not with MTS, which probably indicates that neurosurgeons adequately triage patients for more urgent surgery. Patients scheduled for later surgery usually had an atypical tumor appearance on MRI, often deemed to be a malignantly transformed diffuse glioma of longer existence. Reassuringly, a longer CTS did not result in more complications. Nevertheless, patients with a less-than-optimal KPS score at presentation should probably be scheduled for more urgent surgery to benefit from performance improvement.

The observed large variation in time to surgery between Dutch hospitals is in stark contrast to the relatively limited hospital variation in the previously published outcomes on mortality and survival, and complications and performance changes.[17,18] One factor that could explain this difference is that referral patterns and surgical schedules could facilitate shorter times to surgery in general hospitals compared to university hospitals. Another factor is that hospitals with a lower case load of patients with glioblastoma enable shorter times to surgery, presumably because surgical schedules allow for rescheduling of less urgent neurosurgical procedures in order to prioritize glioblastoma surgery, instead of triaging between brain tumor patients. Other potential factors that contribute to surgical delay could be the number of referring hospitals, resources in ward capacity and personnel, and care prioritization in hospitals. We have no reason to assume a relation between the case load of hospitals and time to surgery from our data. The large variation in times to surgery apparently exists despite consensus on national quality standards.[20] These quality standards were not based on scientific evidence of optimal timings, and our finding that longer CTS was associated with longer survival questions their legitimacy. Conceivably, patients who may benefit from urgent surgery should be better identified to avoid delay before neurosurgical consultation, rather than aiming for an arbitrary cutoff for the whole population. In our population, patients with timely CTS had lower preoperative KPS scores, were indicated for biopsy surgery, and underwent treatment in less recent years. In other studies, a lower KPS score was related to shorter time to surgery, but also a larger tumor volume and a presentation through emergency admission.[10,11] Although less-than-optimal condition (lower KPS score) appears to be a valid selection criterion, the year of treatment is associated likely because of a general increase in glioblastoma surgery in the Netherlands in recent years (Table 1), while a biopsy procedure was associated with shorter CTS because this procedure can be scheduled more easily and requires fewer resources. At the same time, Müller et al. did not observe an association between time to surgery and type of surgery.[10]

Two counteracting phenomena are plausible to understanding the observed relation between time to surgery and glioblastoma survival. First, longer wait times are associated with better survival as patients with unfavorable prognostic characteristics are often recognized for more urgent surgery.[12] The association between the shortest wait times and the poorest survival has been coined the "waiting time paradox," in reference to the popular opinion that surgical delay has a significant and harmful impact on survival.[12,26] We observed this paradox in our CTS analysis. Second, patients with an inadvertently prolonged delay to surgical decompression may have adverse outcomes as a result of tumor growth, progressive symptoms, and possibly irreversible brain damage.[11] These consequences of prolonged wait times were observed in our performance change analysis, showing less improvement in patients with longer times until resection.

The literature on timings in glioblastoma surgery is limited. We found two studies exploring the impact of the route of diagnosis on survival in glioblastoma.[12,27] These studies observed a worse overall survival in patients obtaining a rapid diagnosis by presenting through emergency admission in comparison with routine outpatient services. Another study examined the association between presenting symptoms and survival and reported a longer survival after shorter time to surgery in 63 patients with glioblastoma presenting with a seizure.[11] In our previously published international multicenter study, we found no relation between time from MR scan to surgery and extent of resection, residual tumor volume, postoperative performance change, and survival.[10]

Strengths of this study consist of a comprehensive compulsory national patient registry with standardized definitions. A relatively long time period spanning 6 years of observations from 13 hospitals increases confidence in the external validity of our findings. This quality registry facilitates discussions between neurosurgical teams on quality of glioblastoma care in the Netherlands. The limitation is that the data set was deliberately restricted to essential items to decrease the administrative burden of the registry. As a consequence, we lacked information in these patients before surgery on cause of presentation, other stages of referral, and routes of referral, such as through the emergency department or outpatient clinic. We also lack details on tumor characteristics, as MR scans have not been collaboratively collected for this population. Hospital details on the total number of surgeries, the number of tumor surgeons, and the actual bed capacity are unavailable. Regarding the survival exploration, known prognostic factors such as tumor locations, molecular classifications, and other therapies could not be included in this analysis.[28–31]

Conclusions

Considerable between-hospital variation was observed in the time to glioblastoma surgery between Dutch hospitals. A long time until resection impeded KPS score improvement but was not associated with more complications. Longer survival was observed in patients selected for longer time to surgery after neurosurgical consultation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: De Witt Hamer, De Swart. Acquisition of data: De Witt Hamer, De Swart, Müller, Ardon, Balvers, Bosscher, Bouwknegt, van den Brink, Hovinga, Kloet, Koopmans, Ter Laan, Nabuurs, Nandoe Tewarie, Robe, van der Veer, Viozzi, Wagemakers. Analysis and interpretation of data: De Witt Hamer, De Swart, Müller, Ardon, Balvers, Bosscher, Bouwknegt, van den Brink, Hovinga, Kloet, Koopmans, Ter Laan, Nabuurs, Nandoe Tewarie, Robe, van der Veer, Viozzi, Wagemakers. Drafting the article: De Witt Hamer, De Swart. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: De Witt Hamer. Statistical analysis: De Witt Hamer, Zwinderman. Study supervision: De Witt Hamer.

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