ORIGINAL ARTICLE doi: 10.2176/jns-nmc.2021-0339

Neurol Med Chir (Tokyo) 62, 186-194, 2022 Online February 16, 2022

Perioperative Deep Vein Thrombosis and D-dimer Measurement in Patients with Brain Tumor

Emiko OKAMOTO,[1,2,3] Eiichi ISHIKAWA,[2] Hiroyoshi KINO,[2] Hidehiro KOHZUKI,[2] Narushi SUGII,[2] Hiroyuki NAITO,[3] Takuma HARA,[2] Satoshi HOMMA,[4] Masahide MATSUDA,[2] Takao TSURUBUCHI,[2] Takaaki ISHIKAWA,[2] Yasushi KAWAKAMI,[5] and Hiroyoshi AKUTSU[2]

[1]*Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan*
[2]*Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan*
[3]*Clinical Laboratory, University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan*
[4]*Department of Cardiology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan*
[5]*Department of Clinical Laboratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan*

Abstract

We investigated the appropriate D-dimer cutoff value for each brain tumor type for acute or subacute deep vein thrombosis (DVT) following transcranial brain tumor surgery.

In this single-center retrospective study, a cumulative total of 128 patients who underwent transcranial brain tumor surgery were enrolled and classified into the glioma group, the other intracranial malignant tumor group, and the intracranial benign tumor group. Venous ultrasonography was performed if the D-dimer plasma levels were positive (≥1 μg/mL) before surgery and on postoperative day (POD) 3 or 7.

Of the 128 cases, DVT developed in 32 (25.0%). Among those, acute or subacute DVT was diagnosed in 22 cases on POD 3 and in 8 cases on POD 7. Compared with DVT-negative cases on POD 3, acute or subacute DVT-positive cases on POD 3 revealed a significant increase in the D-dimer level in all groups combined and in the benign tumor group but not in the glioma group. With regard to DVT on POD 3 in all groups, the receiver operating characteristic curve for the D-dimer level on POD 3 demonstrated a cutoff value of 3.3 μg/mL (sensitivity [0.636] and specificity [0.750]). However, if this cutoff value was used in practice, eight cases would be false-negative with a minimum D-dimer level of 1.5 μg/mL.

The D-dimer cutoff value for acute or subacute DVT on POD 3 could be set to 3.3 μg/mL; however, the setting resulted in several false-negative cases. Practically, 1.5 μg/mL of the D-dimer cutoff value on POD 3 might be appropriate to avoid false-negative results.

Keywords: brain tumor surgery, glioma, deep vein thrombosis, D-dimer, complication

Introduction

Pulmonary thromboembolism (PTE) is a life-threatening disease that is characterized by thrombotic occlusion of one or more pulmonary arteries. The acute phase of PTE shows a high mortality rate of 11.9%.[1)] Most emboli in PTE arise from deep vein thrombosis (DVT) in the lower extremities or the pelvis. Since PTE and DVT are a series of pathological conditions, they are called venous thromboembolism (VTE). The incidence of VTE is relatively high (0.5% to 42.6%)[2)] in the field of neurosurgery, and the incidence of DVT in Japan after brain tumor surgery is 21.3%.[3)]

Blood plasma D-dimer measurement followed by ultrasonography of the lower extremities is the main method of

Received October 22, 2021; Accepted December 22, 2021

DVT diagnosis. In brain tumor patients with postoperative DVT, the D-dimer values increase on postoperative days (POD) 1, 2, 3, and 6 with a "zigzagging-rise" pattern.[4] However, the D-dimer values increase not only in VTE but also in various diseases and conditions, including neoplastic diseases, aging, and infections, and also after surgery.[5,6] Therefore, especially in postoperative patients, the setting of the D-dimer cutoff value, in consideration of the D-dimer increase related to surgery-related activation of blood coagulation, is needed to detect postoperative DVT. However, there are few reports on the D-dimer cutoff values for postoperative DVT diagnosis in neurosurgical patients.[5,7] Moreover, the appropriate D-dimer cutoff values for each type of brain tumor and the echographic features of DVT, such as acute, subacute, and chronic phase, are also not specified in most studies. In the present study, we investigated the appropriate D-dimer cutoff value specific to each brain tumor type for acute or subacute (non-chronic) DVT screening following transcranial brain tumor surgery.

Materials and Methods

Patients

A single-center retrospective study was conducted from January 2019 until February 2020. The study was approved by the ethics committee of our institution (R02-016).

A cumulative total of 128 patients who underwent transcranial brain tumor surgery, including 8 who underwent two surgeries at different times (the original patient number was 120, including 56 men and 64 women aged 20-87 years), were enrolled in this study. Those excluded from the study were patients operated with approaches other than open surgery (such as transsphenoidal procedures for pituitary tumors) and patients who had had stroke and were regularly taking anticoagulants or antiplatelet agents. Patients were classified into three groups according to the diagnosis: [1] glioma group (World Health Organization (WHO) grade II, III, or IV); [2] other intracranial malignant tumor group (metastasis, lymphoma, germinoma, atypical meningioma, clear cell meningioma, central neurocytoma, pineal parenchymal tumor with intermediate differentiation, solitary fibrous tumor/hemangiopericytoma); and [3] intracranial benign tumor group (WHO grade I tumors including meningioma and schwannoma and other benign tumors such as a dermoid cyst).

In our hospital, the D-dimer plasma levels (Nanopia D-dimer, Sekisui Medical Co. Ltd., Tokyo, Japan) are routinely measured preoperatively and on POD 3 (2-5) and 7 (6-8). As our hospital's standard practice, venous ultrasonography was performed on the day before surgery for patients with a D-dimer plasma value of ≥1 μg/mL and/or VTE symptoms. In addition, venous ultrasonography was performed between POD 3 and 6 after surgery if the D-dimer plasma levels were positive (≥1 μg/mL) on POD 3, or between POD 7 and 10 if the D-dimer plasma levels were positive (≥1 μg/mL) on POD 7, and/or if a patient had VTE symptoms after surgery even with normal D-dimer level and no VTE symptoms before surgery. Patients with non-chronic DVT were mainly treated with a direct oral anticoagulant (DOAC). Venous ultrasonography for patients with DVT on POD 3 was not repeated on POD 7, even if the D-dimer plasma levels were positive on POD 7. In some patients with DVT and at a high risk of bleeding, anticoagulant therapy was suspended, and ultrasonography was repeated to check whether the DVT extended to the proximal level. No patients in this study received any prophylactic anticoagulation, such as low-molecular-weight heparin, because perioperative thromboprophylaxis for neurosurgical patients is not permitted in Japan.[8]

The DVT risk factors, including age, sex, body mass index (BMI), anesthesia time, operative time, and postoperative motor deficit in the lower extremities, were investigated. In cases where the manual muscle test showed a value of 1-4, the condition was defined as a motor deficit. The use of steroids before venous ultrasonography was also evaluated.

Doppler ultrasonography

To detect DVT, whole-leg compression ultrasound examination was performed by well-trained technicians using the Aplio i800/i900, Aplio a450 (Canon Medical Systems, Tokyo, Japan), or LOGIQ E9 (GE Healthcare, Tokyo, Japan) equipment. The detected DVTs were categorized into distal DVT occurring below the knee and proximal DVT occurring in the iliac, common femoral, femoral, or popliteal vein. Also, DVTs were categorized into acute, subacute, and chronic phases. Acute DVTs were characterized by an increased venous diameter, loss of blood flow around the thrombus, and a low level of echogenicity.[9] Subacute DVTs were defined as normal or increased venous diameter, slight blood flow around the thrombus, and a low level of echogenicity, or as partly bright. Chronic DVTs were characterized by a normal venous diameter, normal or increased blood flow around the thrombus, and a high level of echogenicity.[9]

Data analysis

All values are expressed as medians with interquartile ranges. The postoperative D-dimer plasma levels were compared with preoperative D-dimer plasma levels in each group using Wilcoxon signed-rank test. Moreover, the D-dimer plasma levels were compared between patients with and without DVT using the Wilcoxon rank-sum test or Welch's t-test. The cutoff value was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve. Logistic regression multivariate analysis was employed to determine the predictors of DVT.

The measurements were analyzed using the JMP statistical software program version 14 (SAS Institute Inc., Cary,

Table 1 The number of examinations and characteristics of DVT in groups

Group	Ultrasonography performed, n (%)	DVT firstly detected after surgery, n (%)	Non-chronic DVT, n (%)	Chronic DVT, n (%)	Proximal DVT, n (%)	Distal DVT, n (%)
Glioma						
Total	56	15	13	2	1	14
POD 3	37 (66.1)	10 (66.7)	10 (76.9)	0 (0)	1 (100)	9 (64.3)
POD 7	19 (33.9)	5 (33.3)	3 (23.1)	2 (100)	0 (0)	5 (35.7)
Other intracranial malignant tumors						
Total	18	2	2	0	0	2
POD 3	13 (72.2)	1 (50)	1 (50)	0 (0)	0 (0)	1 (50)
POD 7	5 (27.8)	1 (50)	1 (50)	0 (0)	0 (0)	1 (50)
Intracranial benign tumors						
Total	54	15	15	0	1	14
POD 3	40 (74.1)	11 (73.3)	11 (73.3)	0 (0)	1 (100)	10 (71.4)
POD 7	14 (25.9)	4 (26.7)	4 (26.7)	0 (0)	0 (0)	4 (28.6)
All groups (total)	128	32	30	2	2	30
POD 3	90 (70.9)	22 (68.8)	22 (73.3)	0 (0)	2 (100)	20 (66.7)
POD 7	38 (29.1)	10 (31.2)	8 (26.7)	2 (100)	0 (0)	10 (33.3)

Values are expressed as numbers of examinations (%).
DVT, deep vein thrombosis
POD, postoperative day

NC, USA). For all statistical tests, a *P*-value of <0.05 was considered significant (based on two-tailed tests).

Results

Properties of DVT

Out of all 128 cases, DVT developed in 32 (25.0%), including 22 (68.8%) observed on POD 3 and 10 (31.2%) on POD 7 (Table 1). Among those, non-chronic DVT was observed in 22 cases on POD 3 and in 8 on POD 7. The proximal and distal DVTs on POD 3 were observed in 2 and 20 cases, respectively. The DVTs observed on POD 7 were only in the distal part (Table 1). No patients in this study had symptomatic PTE.

In the glioma group, DVT developed in 15 out of 56 (26.8%) cases, which consisted of 10 cases (66.7%) on POD 3 and 5 (33.3%) on POD 7 (Table 1). Of these, non-chronic DVT was observed in 10 cases on POD 3 and in 3 on POD 7. Although the preoperative D-dimer plasma levels were negative (<1 μg/mL), 2 cases had chronic DVT on POD 7, which might have developed preoperatively.

In the other intracranial malignant tumor group, 2 out of 18 (11.1%) cases were diagnosed with DVT, observed in 1 case (50%) on POD 3 and 1 case (50%) on POD 7. Both DVTs were in the non-chronic phase (Table 1). In the benign tumor group, DVT developed in 15 out of 54 (27.8%) cases, observed in 11 cases (73.3%) on POD 3 and 4 cases (26.7%) on POD 7. Those DVTs were in the non-chronic phase (Table 1).

D-dimer change in DVT-positive and DVT-negative cases

In non-chronic DVT-positive cases on POD 3, the D-dimer level significantly increased on both POD 3 and 7 compared with the level before surgery in all groups, the glioma group and the benign tumor group (Fig. 1A, B and D left). In the DVT-negative cases on POD 3, the D-dimer level also significantly increased both on POD 3 and 7 compared with that before surgery in all cases (Fig. 1A-D left).

In non-chronic DVT-positive cases on POD 7, the D-dimer level significantly increased on POD 7 compared with that before surgery in all groups (Fig. 1A right), although the D-dimer levels were not significantly higher on POD 7 across the three groups (Fig. 1B-D right).

Comparison of DVT-positive and DVT-negative cases

Of the entire cohort, a significant increase in the D-dimer level ($P = 0.011$) was observed among the 22 non-chronic DVT-positive cases on POD 3 (45.5% in the glioma group, 4.5% in the other intracranial malignant tumor group, and 50% in benign tumor group) compared with the 68 DVT-negative cases. There was also a significant increase in the difference of the D-dimer level between POD 3 and that before surgery ($P = 0.017$, Table 2). Furthermore, the patients with non-chronic DVT were significantly older ($P < 0.001$). In the logistic regression analysis, there were no independent risk factors for the incidence of non-chronic DVT. Compared with the 27 DVT-negative

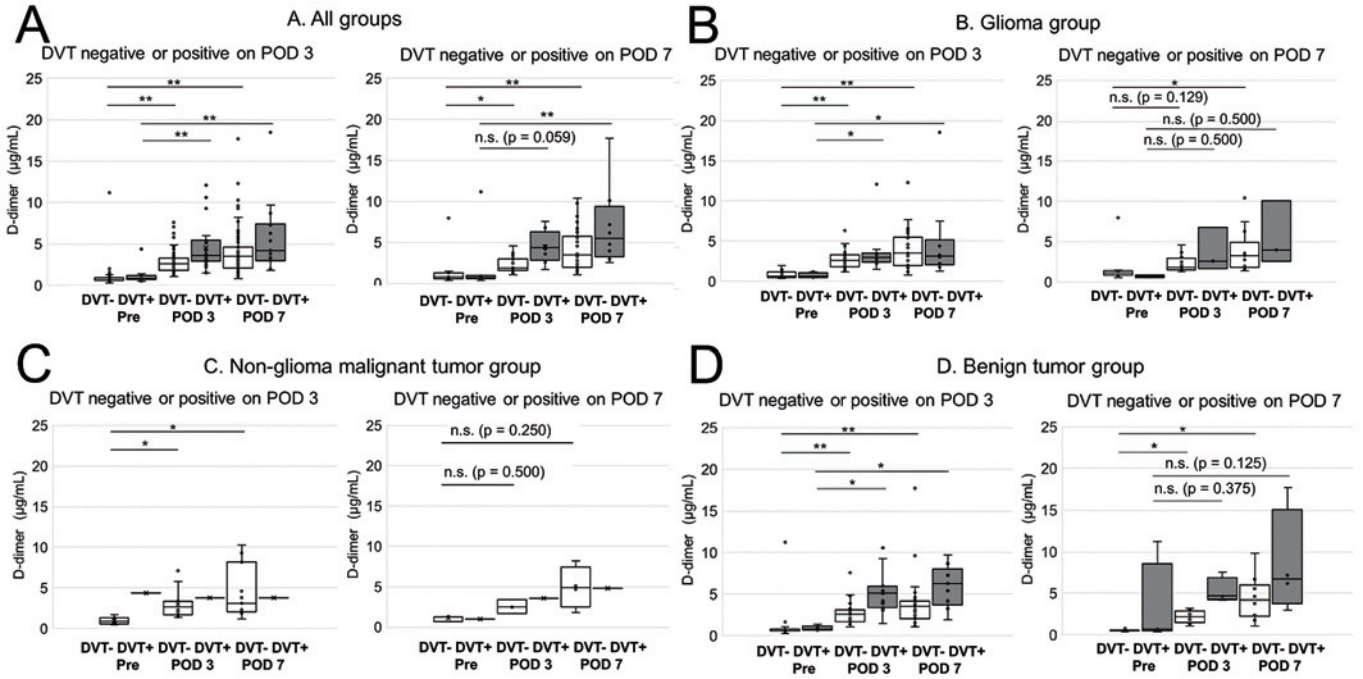

Fig. 1 A. D-dimer level changes in all groups. Left: DVT-negative (n = 68) and DVT-positive (n = 22) cases with acute or subacute (non-chronic) DVT on POD 3. Right: DVT-negative (n = 27) and DVT-positive (n = 8) cases with non-chronic DVT on POD 7.
B. D-dimer level changes in the glioma group. Left: DVT-negative (n = 27) and DVT-positive (n = 10) cases with non-chronic DVT on POD 3. Right: DVT-negative (n = 13) and DVT-positive (n = 3) cases with non-chronic DVT on POD 7.
C. D-dimer level changes in the non-glioma malignant tumor group. Left: DVT-negative (n = 12) and DVT-positive (n = 1) cases with non-chronic DVT on POD 3. Right: DVT-negative (n = 4) and DVT-positive (n = 1) cases with non-chronic DVT on POD 7.
D. D-dimer level changes in the benign tumor group. Left: DVT-negative (n = 29) and DVT-positive (n = 11) cases with non-chronic DVT on POD 3. Right: DVT-negative (n = 10) and DVT-positive (n = 4) cases with non-chronic DVT on POD 7.
***P < 0.05, ** P < 0.001 and not significant (n.s.) in Wilcoxon's signed-rank test.**

cases on POD 7, there was a significant increase in the difference of the D-dimer level between POD 7 and that before surgery (P = 0.020) in 8 DVT-positive cases with non-chronic DVT, although the D-dimer level was not significantly higher on POD 7 (Supplementary data 1). In the logistic regression analysis, there were also no independent risk factors for the incidence of non-chronic DVT on POD 7.

In the glioma group, in 10 non-chronic DVT-positive cases on POD 3, there were no significant difference in the various factors, including the D-dimer level on POD 3, compared with 27 DVT-negative cases, except for the patient age (P = 0.005, Table 3). The WHO grade also had no effect on the presence of postoperative DVT (WHO grade 4 versus grades 2 and 3, Fisher's exact test, P = 0.160). Non-chronic DVT-positive and DVT-negative cases on POD 7 in the glioma group and non-chronic DVT-positive and DVT-negative cases on POD 3 and 7 in the other malignant tumor group were not analyzed due to the small number of cases.

With regard to the benign tumor group, in 11 non-chronic DVT-positive cases on POD 3, the increase in the D-dimer level was significant (P = 0.011) compared with the 29 DVT-negative cases. The difference between the D-dimer level on POD 3 and that before surgery and the D-dimer level ratio between POD 3 level and that before surgery were also significant (P = 0.006 and P = 0.013, respectively, Table 3). In addition, patients with non-chronic DVT were older (P = 0.023). On logistic regression analysis, there were also no independent risk factors for the incidence of non-chronic DVT.

No significant difference was observed in the anesthesia or operative time between the DVT-positive and non-DVT cases among all cases, the glioma group, and the benign tumor group (Tables 2 and 3). Furthermore, there was no difference in the anesthesia time between the benign tumor group (DVT-screened 40 cases on POD 3 including 11 DVT-positive cases, median time of 626 min) and the glioma group (DVT-screened 37 cases on POD 3 including 10 DVT-positive cases, median time of 559 min) (Wilcoxon rank-sum test, P = 0.080). In addition, the operative time in DVT-screened cases on POD 3 of the benign tumor group (40 cases, median time of 492 min) tended to be longer than that of the glioma group (37 cases, median time of 408 min), although there was no significant difference (Wilcoxon's rank-sum test, P = 0.127). Non-chronic

Table 2 Comparison of non-chronic DVT-positive and DVT-negative cases on POD 3 (to 6) in all groups screened using the positive D-dimer level on POD 3

Variable	DVT (non-chronic)	No DVT	*P*-value	OR (95% CI)
Number of examinations on POD 3 (to 6)	22	68		
Preop D-dimer levels (μg/mL), median (range)	0.8 (0.5–4.4)	0.65 (0.3–11.2)	0.814††	
D-dimer levels on POD 3 (μg/mL), median (range)	3.6 (1.5–12.1)	2.6 (1.1–7.6)	**0.011**††	
Difference in the D-dimer level between POD 3 and that before surgery (μg/mL), median (range)	2.9 (–0.6–11.6)	1.7 (–3.6–5.8)	**0.017**††	
Ratio between the D-dimer level on POD 3 and that before surgery, median (range)	5.1 (0.9–24.2)	3.3 (0.7–16.3)	0.109††	
Age, median (range)	70 (48–83)	56 (20–87)	**<0.001**††	
BMI, median (range)	23 (19–28)	23 (16–32)	0.252†	
Anesthesia time (minutes), median (range)	599 (230–763)	550 (147–934)	0.775†	
Operative time (minutes), median (range)	476 (132–681)	397 (43–809)	0.642†	
Malignant tumors, Yes/No	11/11	39/29	0.156 †††	0.411 (0.113–1.361)
Sex, M/F	13/9	33/35	0.205 †††	2.027 (0.694–6.318)
Postop motor deficit, Yes/No	9/13	19/49	0.119†††	2.574 (0.795–8.853)
Preop or postop steroid use, Yes/No	7/15	18/50	0.387†††	1.626 (0.523–4.876)

Bold font indicates statistical significance.
† Wilcoxon rank-sum test
†† Welch's t-test
††† Logistic regression multivariate analysis
BMI, body mass index
DVT, deep vein thrombosis
POD, postoperative day
OR, odds ratio

DVT-positive and DVT-negative cases on POD 7 were not analyzed due to the small number of cases.

Calculating the D-dimer cutoff values

Regarding non-chronic DVT on POD 3, the ROC curve for the D-dimer level showed the shortest distance to the top-left corner when the cutoff value was set to 3.3 μg/mL, marked in the diagram with balanced sensitivity (63.6%) and specificity (75.0%, Fig. 2A left). The positive predictive value (PPV) and negative predictive value (NPV) were 45.2% and 86.4%, respectively. When these levels were used as cutoff values, the results of eight patients (six in the glioma group and two in the benign tumor group) turned to be false-negative (Supplementary data 2). The minimum D-dimer level on POD 3 was 1.5 μg/mL among the false-negative cases, and the sensitivity was 100% with this cut-off value (Supplementary data 3). Additionally, the ROC curve for the difference between the D-dimer on POD 3 and that before surgery showed a cutoff value of 2.5 μg/mL with balanced sensitivity (70.0%) and specificity (75.8%, Fig. 2A right).

In the benign tumor group, the ROC curve for the D-dimer level on POD 3, which significantly increased in non-chronic DVT-positive cases, showed a cutoff value of 3.1 μg/mL, marked in the diagram with balanced sensitivity (90.9%) and specificity (75.9%, Fig. 2B left). The PPV and NPV were 58.8% and 95.7%, respectively. Moreover, the ROC curve for the difference between the D-dimer on POD 3 and that before surgery showed a cutoff value of 2.6 μg/mL, marked in the diagram with balanced sensitivity (81.8%) and specificity (78.6%, Fig. 2B middle). Also, the cutoff value of 4.67 in the D-dimer ratios on POD 3 com-

Table 3 Comparison of non-chronic DVT-positive and DVT-negative cases on POD 3 (to 6) in the glioma and benign tumor group screened using the positive D-dimer level on POD 3

Variable	DVT (non-chronic)		No DVT		*P*-value		OR (95% CI)	
Group	Glioma	Benign tumor	Glioma	Benign tumor	Glioma	Benign tumor	Glioma	Benign tumor
Number of examinations on POD 3 (to 6)	10	11	27	29				
Preop D-dimer level (μg/mL), median (range)	0.7 (0.5–1.2)	0.8 (0.7–1.4)	0.7 (0.4–2.0)	0.6 (0.3–11.2)	0.789†	0.709††		
D-dimer level on POD 3 (μg/mL), median (range)	3.0 (1.5–12.1)	5.1 (1.5–10.6)	2.6 (1.2–6.3)	2.6 (1.1–7.6)	0.333††	**0.011**††		
Difference in the D-dimer level between POD 3 and that before surgery (μg/mL), median (range)	2.5 (0.3–11.6)	4.4 (0.7–9.4)	1.9 (0.2–5.8)	1.7 (−3.6–4.6)	0.368††	**0.006**††		
Ratio between the D-dimer level on POD 3 and that before surgery, median (range)	5.2 (1.3–24.2)	5.4 (1.9–8.3)	3.5 (1.1–12.6)	3.4 (0.7–16.3)	0.352††	**0.013**†		
Age, median (range)	71.5 (48–83)	67 (53–80)	50 (24–81)	61 (23–78)	**0.005**†	**0.023**††		
BMI, median (range)	25 (19–28)	23 (20–26)	22 (16–29)	23 (17–32)	0.154†	0.523†		
Anesthesia time (minutes), median (range)	501 (230–763)	675 (483–750)	570 (217–915)	569 (222–934)	0.252†	0.287††		
Operative time (minutes), median (range)	337 (132–681)	535 (381–576)	433 (89–781)	424 (113–809)	0.330†	0.153††		
Sex, M/F	7/3	6/5	17/10	7/22	0.744 †††	0.058 †††	1.309 (0.260–6.597)	4.210 (0.924–19.16)
Postop motor deficit, Yes/No	7/3	1/10	13/14	3/26	0.262†††	0.806 †††	2.444 (0.512–11.659)	0.731 (0.057–9.364)
Preop or postop steroid use, Yes/No	3/7	3/8	6/21	6/23	0.608 †††	0.517 †††	1.551 (0.289–8.324)	1.787 (0.314–10.18)

Bold font indicates statistical significance.
† Wilcoxon rank-sum test
†† Welch's t-test
††† Logistic regression multivariate analysis
BMI, body mass index
DVT, deep vein thrombosis
POD, postoperative day
OR, odds ratio

pared with that before surgery showed balanced sensitivity (72.7%) and specificity (75.0%, Fig. 2B right).

Discussion

DVT developed in approximately 25% of patients who underwent transcranial brain tumor surgery. Of these, 68.8% of DVT-positive cases were observed on POD 3, and all of them were in the non-chronic phase. Our results suggest that DVT screening based on the increase in the D-dimer level on POD 3 is useful for the early detection of non-chronic DVT.

The frequencies of DVT after surgery were 26.8% and 11.1% in the glioma and other intracranial malignant tumor groups, respectively. In general, a prothrombotic state occurs in cancer patients due to the tumor cells' procoagulant production. For example, tissue factor expression is significantly stronger in ovarian cancer patients with VTE compared with those without it.[10] In our study, DVT-positive cases were also frequently observed following surgery in the benign tumor group (27.8%). A previous study has reported that the incidence of DVT in malignant tumors is lower compared with that in patients with meningioma due to the long operation time in meningioma

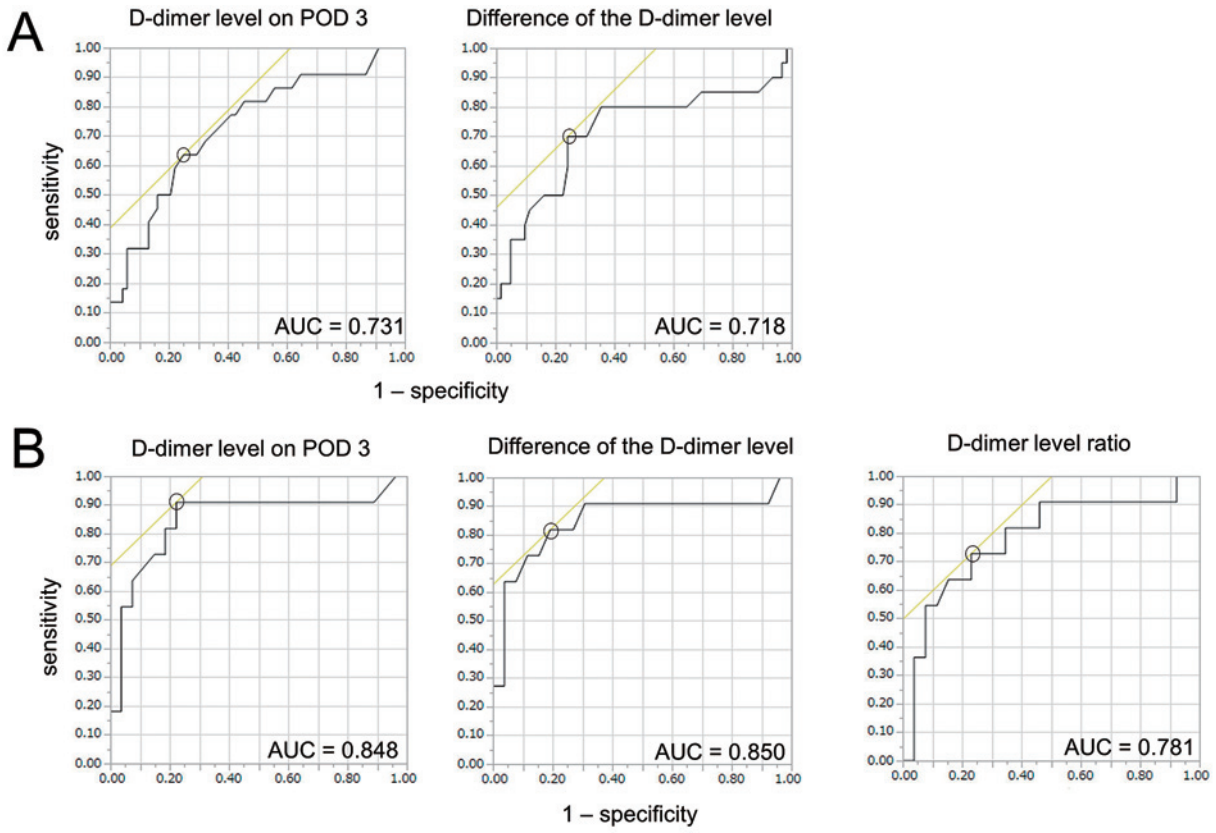

Fig. 2 A. The ROC curve for the D-dimer level in all groups with non-chronic DVT (n = 22) vs. those without DVT (n = 68).
Left: The ROC curve for the D-dimer level on the third day after surgery. The cutoff value of 3.3 μg/mL marked in the diagram showed balanced sensitivity (63.6%) and specificity (75.0%).
Right: The ROC curve for the difference of the D-dimer level between POD 3 and that before surgery. The cutoff value of 2.5 μg/mL, marked in the diagram, shows balanced sensitivity (70.0%) and specificity (75.8%).
B. The ROC curve for the D-dimer level in patients diagnosed with intracranial benign tumors with DVT (n = 11) vs. those without DVT (n = 29).
Left: The ROC curve for the D-dimer level on the third day after surgery. The cutoff value of 3.1 μg/mL marked in the diagram showed balanced sensitivity (90.9%) and specificity (75.9%).
Middle: The ROC curve for the difference of the D-dimer level between POD 3 and that before surgery. The cutoff value of 2.6 μg/mL marked in the diagram showed balanced sensitivity (81.8%) and specificity (78.6%).
Right: The ROC curve for the D-dimer level ratio between POD 3 and that before surgery. The cutoff value of 4.67 marked in the diagram showed balanced sensitivity (72.7%) and specificity (75.0%).

patients.[7] In our study, the operative time in the benign tumor group tended to be longer than that in the glioma group. However, no significant difference was observed in the anesthesia or operative time between DVT-positive and non-DVT cases among all cases, the glioma group, and the benign tumor group (Tables 2 and 3). Further studies are required to reveal the mechanisms of DVT formation in patients with glioma and benign tumor.

Non-chronic DVT-positive cases on POD 3 exhibited a significant increase in the D-dimer level on both POD 3 and 7 compared with that before surgery among all groups, the glioma group, and the benign tumor group. The DVT-negative cases on POD 3 also showed a significant increase in the D-dimer level on both POD 3 and 7 compared with that before surgery, because the D-dimer level was apparently influenced by the surgical procedure. Compared with the DVT-negative cases on POD 3, non-chronic DVT-positive cases showed a significant increase in the D-dimer level in all groups and in the benign tumor group but not in the glioma group; therefore, we were not able to calculate the D-dimer cutoff value for the glioma group. In the benign tumor group, the optimal D-dimer cutoff value on POD 3 was 3.1 μg/mL with a sensitivity of 90.9% and a specificity of 75.9%. In all groups (consisting of 45.5% in the glioma group, 4.5% in the other intracranial malignant tumor group, and 50% in the benign tumor group), the D-dimer cutoff value on POD 3 was 3.3 μg/mL with sensitivity and specificity of 63.6% and 75.0%, respectively, and was lower than in the benign tumor group due to the influence of the glioma group. The sensitivity and

specificity are suggested to be optimized by calculating the D-dimer cutoff value for each disease. A previous study has reported that the sensitivity and specificity for VTE with a D-dimer cutoff value of 2.0 μg/mL are 95.3% and 74.1%, respectively.[5] Compared with our study, this higher sensitivity and specificity could be due to the fact that their study included VTE-positive cases with a higher rate of benign tumors (69.8%) and a lower rate of glioma (11.6%).[5] In the present study, if the D-dimer cutoff value on POD 3 was set to 3.3 μg/mL across all groups, there were eight false-negative cases with a minimum D-dimer level of 1.5 μg/mL. In clinical practice, the D-dimer value of 1.5 μg/mL on POD 3 with a sensitivity of 100% might be appropriate as a cutoff value to reduce false-negative cases. In the DVT-positive cases on POD 3, the difference of the D-dimer level between POD 3 and that before surgery was also significantly increased. The ROC curve for the difference of the D-dimer level exhibited cutoff values of 2.5 and 2.6 μg/mL in all groups and in the benign tumor group, respectively. Since the D-dimer value could be affected by postoperative inflammation, it might be better to examine the change of the D-dimer than to examine only the D-dimer. The validity of the cutoff value needs to be verified in a prospective study.

Compared with DVT-negative cases on POD 7, non-chronic DVT-positive cases in all groups exhibited no significant increase in the D-dimer level mainly due to the small number of DVT-positive cases. Natsumeda et al. has reported that the D-dimer level in DVT-positive cases significantly increases on POD 7 compared with that in DVT-negative cases, and in this study, the D-dimer cutoff value on POD 7 was set to 2.65 μg/mL with a sensitivity of 85.7% and a specificity of 72.3%.[7] In our study, non-chronic DVT-positive cases on POD 7 showed a significant increase in the D-dimer level compared with that before surgery in all groups. Further studies are needed to reveal the D-dimer cutoff value on POD 7.

In our study, aging was a risk factor for the initially diagnosed DVT after surgery. A previous study has demonstrated that the VTE risk factors in patients following craniotomy are aging, BMI, tumor history, operative time, chronic steroid use, presence of motor deficit, Wells score, etc.[2,5,7,11,12] As a limitation of our study, the D-dimer plasma levels were not measured at exactly the same time for each patient before and after surgery. Moreover, the small number of cases affected the statistical outcomes, which resulted in a lack of significance in cases of operation and anesthesia time, steroid use, and postoperative motor deficit. In addition, other coagulation markers of DVT can be investigated.

In conclusion, postoperative DVT was diagnosed in approximately 25% of cases in patients following transcranial brain tumor surgery. Of these, 68.8% DVT-positive cases were detected on POD 3, and all of them were in the non-chronic phase. Therefore, DVT screening based on an increase in the D-dimer level on POD 3 may be useful for the early detection of non-chronic DVT. In our study, the D-dimer cutoff value on POD 3 for DVT detection in brain tumor patients was 3.3 μg/mL with a sensitivity of 63.6% and specificity of 75.0%; however, these data retrospectively led to several false-negative results. Practically, 1.5 μg/mL of the D-dimer cutoff value on POD 3 should be used to avoid such false-negative results. Future prospective studies are required to confirm the optimal and efficient D-dimer cutoff value on POD 3 to predict DVT with higher sensitivity and specificity.

Okamoto E and Ishikawa E contributed equally to this work as first authors.

Supplementary Material

https://doi.org/10.2176/jns-nmc.2021-0339

Acknowledgments

We thank Dr. Alexander Zaboronok, Department of Neurosurgery, Faculty of Medicine of the University of Tsukuba for professional and English revision.

Funding

A research funding (AS2020A000259222) from Otsuka pharmaceutical cooperation was received for this research.

Conflicts of Interest Disclosure

No conflict(s) of interest.

References

1) Sakuma M, Okada O, Nakamura M, et al.: Japanese Society of Pulmonary Embolism Research: Recent developments in diagnostic imaging techniques and management for acute pulmonary embolism: multicenter registry by the Japanese Society of Pulmonary Embolism Research. *Intern Med* 42: 470-476, 2003
2) Rinaldo L, Brown DA, Bhargav AG, et al.: Venous thromboembolic events in patients undergoing craniotomy for tumor resection: incidence, predictors, and review of literature. *J Neurosurg* 32: 10-21, 2019
3) Nakano F, Matsubara T, Ishigaki T, et al.: Incidence and risk factor of deep venous thrombosis in patients undergoing craniotomy for brain tumors: A Japanese single-center, retrospective study. *Thromb Res* 165: 95-100, 2018
4) Guo X, Zhang F, Wu Y, et al.: Coagulation alteration and deep vein thrombosis in brain tumor patients during the perioperative period. *World Neurosurg* 114: e982-e991, 2018
5) Prell J, Rachinger J, Smaczny R, et al.: D-dimer plasma level: a reliable marker for venous thromboembolism after elective craniotomy. *J Neurosurg* 119: 1340-1346, 2013
6) Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bounameaux H: D-dimer plasma concentration in various clini-

cal conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. *Thromb Res* 69: 125-130, 1993
7) Natsumeda M, Uzuka T, Watanabe J, et al.: High incidence of deep vein thrombosis in the perioperative period of neurosurgical patients. *World Neurosurg* 112: e103-e112, 2018
8) JCS Joint Working Group: Guidelines for diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2017)
9) Meissner MH, Moneta G, Burnand K, et al.: The hemodynamics and diagnosis of venous disease. *J Vasc Surg* 46: 4S-24S, 2007
10) Uno K, Homma S, Satoh T, et al.: Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer. *Br J Cancer* 96: 290-295, 2007
11) Rethinasamy R, Alias A, Kandasamy R, Raffiq A, Looi MC, Hillda T: Deep vein thrombosis and the neurosurgical patient. *Malays J Med Sci* 26: 139-147, 2019
12) Shi S, Cheng J, Chen H, Zhang Y, Zhao Y, Wang B: Preoperative and intraoperative predictors of deep venous thrombosis in adult patients undergoing craniotomy for brain tumors: A Chinese single-center, retrospective study. *Thromb Res* 196: 245-250, 2020

Corresponding author: Eiichi Ishikawa, M.D., Ph.D.
Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.
e-mail: e-ishikawa@md.tsukuba.ac.jp