The role of preoperative deep vein thrombosis screening in neurooncology

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OBJECTIVE Venous thromboembolism (VTE) is a major cause of morbidity in patients undergoing neurosurgical intervention. The authors postulate that the introduction of a routine preoperative deep vein thrombosis (DVT) screening protocol for patients undergoing neurosurgical intervention for brain tumors would result in a more effective diagnosis of DVT in this high-risk subgroup, and subsequent appropriate management of the condition would reduce pulmonary embolism (PE) rates and improve patient outcomes.

METHODS The authors conducted a prospective study of 115 adult patients who were undergoing surgical intervention for a brain tumor. All patients underwent preoperative lower-limb Doppler ultrasonography scanning for DVT screening. Patients with confirmed DVT underwent a period of anticoagulation therapy, which was stopped prior to surgery. An inferior vena cava (IVC) filter was inserted to cover the perioperative period during which anticoagulation therapy was avoided due to bleeding risk before restarting the therapy at a later date. Patients underwent follow-up performed by a neurooncology multidisciplinary team, and subsequent complications and outcomes were recorded.

RESULTS Seven (6%) of the 115 screened patients had DVT. Of these patients, one developed postoperative PE, and another had bilateral DVT postoperatively. None of the patients without preoperative DVT developed VTE postoperatively. Age, symptoms of DVT, and previous history of VTE were significantly higher in the group with preoperative DVT. There were no deaths and no complications from the anticoagulation or IVC filter insertion.

CONCLUSIONS Preoperative screening for DVT is a worthwhile endeavor in patients undergoing neurosurgical intervention. A multidisciplinary approach in management of anticoagulation and IVC filter insertion is safe and can minimize further VTE in such patients.

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KEY WORDS deep vein thrombosis; pulmonary embolus; neurooncology; brain tumor; screening; oncology

VENOUS thromboembolism (VTE) is a major cause of morbidity in patients undergoing neurosurgical intervention. The incidence rates of VTE have been shown to be considerably higher in patients presenting with neoplastic disease.10 Studies from the early 1990s estimated an incidence of deep vein thrombosis (DVT) of 18%–50% and pulmonary embolism (PE) of 0%–25% in neurosurgical patients.10 More recent retrospective series have reported the incidence rate of DVT in neurooncology patients at 3.2%–23%,1,13 with a PE incidence rate of 1.8%.13 PE remains a significant cause of morbidity, higher than that for general neurosurgery patients. In the immediate 12-month period prior to the present study, we observed that the incidence of perioperative VTE in all neurosurgi-
cal patients at our center was approximately 1% and approximately 2% in neurooncology patients. This was at a time during which DVT screening in patients with brain tumors was not routine.

The reasons for this predisposition of developing VTE are multifactorial and not fully understood. VTE formation is thought to be due to the interplay of various events. The induction of vascular endothelial cell damage and the release of prothrombotic factors causing activation of the coagulation cascade, caused by the tumor mass itself and the surgical insult, are major contributing factors. Immobilization due to tumor-related motor deficits and intraoperative muscle relaxants may result in venous stasis, thus potentiating thrombogenesis. This is compounded by the fact that neurosurgical patients are often not prescribed pharmacological VTE prophylaxis postoperatively due to the concerns about the increased risk of hemorrhage.

The most catastrophic complication of DVT is PE, and lower-limb DVTs have been reported to account for as many as 90% of all PEs. This has important implications, given the overall mortality associated with PE. Studies have shown that untreated acute PE carries a mortality rate of 15%–30%. Of this group of patients with acute PE who die, it is reported that up to 10% die suddenly, whereas a further two-thirds die within 2 hours of presentation. This is much higher than the mortality of diagnosed and treated PE, which is 8%. The Wells score or serum D-dimer levels have a high negative predictive value in oncology patients, but a low Wells score and a low D-dimer level are not a common combination in this group of patients, as they frequently have other reasons for leg swelling and pain, and malignancy and chemotherapy can render the D-dimer test positive in the absence of DVT.

The mainstay of treating DVT in the general population is by anticoagulation. This has traditionally been with oral coumarins, although occasionally with subcutaneous unfractionated or low-molecular-weight heparin. Recent trends have moved toward the frontline use of direct oral anticoagulant agents.

If neurosurgical intervention is to be undertaken in a patient with a known DVT or PE, a risk-benefit judgment must be made regarding the risk of complications from VTE versus intracranial hemorrhage. If preoperative pharmacological treatment is indicated, it must be tightly regulated and sufficiently short acting to allow planning for timing of surgery. Inferior vena cava (IVC) filters have been shown to reduce the risk of PE in patients with DVT who have contraindications to anticoagulation therapy. It also offers some protection against PE in the immediate postoperative period, during which the patient does not receive anticoagulant agents due to the bleeding risks. We employ a multidisciplinary team (MDT) approach for the management of such cases, comprising the hematologist, neurosurgery, and interventional radiology services. We use a combination of pharmacological anticoagulation therapy and an IVC filter to facilitate safe neurosurgical intervention in patients with DVT.

We postulate that the introduction of a routine preoperative DVT screening protocol followed by the MDT for patients undergoing neurosurgical intervention for brain tumors will result in a more effective diagnosis of DVT in this high-risk subgroup, and subsequent appropriate management of this would reduce PE rates and improve patient outcome.

Methods
Protocol
We conducted a prospective study of all neurosurgical oncology patients attending our preassessment clinic between April 2014 and January 2015. It is our standard practice to examine all neurooncology patients requiring surgery in this clinic except for those who need emergency operations, which represents less than 5% of our caseload. As part of the preassessment process, all patients undergo preoperative routine DVT screening via bilateral lower-limb venous Doppler ultrasonography. All patients were given mechanical prophylaxis using compression stockings intraoperatively and postoperatively until they were discharged from the hospital or fully ambulatory.

Our study population comprised adults older than 18 years undergoing a biopsy or craniotomy for a cranial tumor. Primary and secondary tumors were included, as were supra- and infratentorial tumors. During the patient consent process, all patients also provided consent for DVT screening. At the time the data were analyzed, patients underwent follow-up by the MDT for a median duration of 4 months (range 1–12 months). Demographic details, performance status, histology, and comorbidities were recorded, and the Charlson Comorbidity Index (CCI) was calculated for each patient. Any patient with a clinical suspicion for PE pre- or postoperatively underwent CT pulmonary angiography. Patients with proven DVT on ultrasonography were managed with an IVC filter inserted by our interventional radiologists, as well as additional anticoagulation, the dose and timing of which were decided on by our hematologists on a case-by-case basis. The IVC filters were removed as an elective procedure several months after surgery once the risk of further thromboembolic events was deemed to be sufficiently low. All patients with no preoperative findings on DVT screening received daily prophylactic-dose enoxaparin starting the day after surgery, which was continued until discharge from the hospital.

Statistical Analysis
Statistical analyses were performed in which the differences between the groups with and without preoperative DVT were compared. The mean age, median CCI, and median WHO performance scores were compared using the Student t-test. Tumor type and smoking status between the 2 groups were compared using the 2-proportion t-test (z-test). Fisher’s exact test was used to compare the number of males and females and the number of patients who were symptomatic and asymptomatic at presentation between the 2 groups. These tests were conducted using Prism (version 6.00, GraphPad).

Results
Of the 115 patients undergoing routine preoperative DVT Doppler screening, 7 patients (6%) had DVT. Five of these 7 patients had proximal DVTs, and 2 patients had
distal DVTs. The remaining patients (108 [94%]) did not have a preoperative DVT on screening. No patient had a preoperative PE, but 1 patient (0.9%) developed a postoperative PE; this patient also had preoperative DVT on screening (Fig. 1).

Patient Characteristics

Table 1 shows the differences in age, sex, and comorbidity statuses of patients with preoperative DVT in comparison with those without preoperative DVT. As part of our comorbidity assessment, we also examined previous VTE history and smoking status, which consisted of 3 domains: current smokers, non–current smokers (including never-smokers and ex-smokers), and unknown smoking status. We found that increased age, previous history of VTE, and the presence of symptoms were more common in the group with preoperative DVT than in those without preoperative DVT findings. These results were statistically significant (p = 0.0321, p = 0.0088, and p = 0.0181, respectively).

Tumor Type

In the group with preoperative DVT (n = 7), 3 patients were diagnosed with glioblastoma, 3 with meningioma, and 1 patient with anaplastic oligodendroglioma. In our cohort, there was no propensity toward DVT in patients with meningioma compared with other tumor types.

Of the group without preoperative DVT (n = 108), 36 presented with glioblastoma, 30 with meningioma, 16 with metastatic tumors, and 26 with other tumors. Of the metastatic tumors, 4 were of breast origin, 3 from the gastrointestinal tract, 3 from the lung, 1 of ovarian origin, and 2 were metastatic malignant melanoma deposits; the origin was unknown for 3 tumors. Other malignancies in the remaining 26 patients were astrocytomas (n = 8), oligodendrogliomas (n = 3), and other tumors (n = 15).

![Flow diagram showing key differences in clinical outcome between patients with and without preoperative findings of DVT.](image)

**FIG. 1.** Flow diagram showing key differences in clinical outcome between patients with and without preoperative findings of DVT. Figure is available in color online only.

**TABLE 1.** Summary of key demographic and comorbidity differences between patients with and without preoperative DVT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>w/ Preop DVT (n = 7)</th>
<th>w/o Preop DVT (n = 108)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<td></td>
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<tr>
<td>Mean age ± SEM in yrs</td>
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<td>56.19 ± 1.282</td>
<td>0.0321*</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<td>48 (44)</td>
<td>0.6995</td>
</tr>
<tr>
<td>Female</td>
<td>3 (43)</td>
<td>60 (56)</td>
<td>0.6995</td>
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<tr>
<td>Smoking status</td>
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<td></td>
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<tr>
<td>Current smokers</td>
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<td>17 (16)</td>
<td>0.2543</td>
</tr>
<tr>
<td>Non–current smokers</td>
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<td>63 (58)</td>
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<td>28 (26)</td>
<td>0.3271</td>
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<td>Comorbidities</td>
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<tr>
<td>Median CCI (range)</td>
<td>5 (3–5)</td>
<td>4 (1–11)</td>
<td>0.9939</td>
</tr>
<tr>
<td>Median WHO performance score (range)</td>
<td>1 (0–1)</td>
<td>1 (0–4)</td>
<td>0.6960</td>
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<td>Previous VTE history</td>
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<td>1 (1)</td>
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<tr>
<td>Tumor type</td>
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<td></td>
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<tr>
<td>Glioblastoma</td>
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<td>36 (33)</td>
<td>0.6031</td>
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<tr>
<td>Meningioma</td>
<td>3 (43)</td>
<td>30 (28)</td>
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<tr>
<td>Metastatic</td>
<td>0 (0)</td>
<td>16 (15)</td>
<td>0.2713</td>
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<tr>
<td>Other</td>
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<td>26 (24)</td>
<td>0.5552</td>
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<tr>
<td>Presentation</td>
<td></td>
<td></td>
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<tr>
<td>Symptomatic</td>
<td>2 (29)</td>
<td>2 (2)</td>
<td>0.0181*</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5 (71)</td>
<td>106 (98)</td>
<td>0.0181*</td>
</tr>
</tbody>
</table>

Values are presented as the number of patients (%) unless stated otherwise. Percentages may not total 100% due to rounding.

* Statistically significant.
Patients with more aggressive tumors underwent anticoagulation therapy ranging between 1 and 3 months. Of the 3 patients reporting DVT-like symptoms, 2 patients had a DVT. One patient complained of chest pain and shortness of breath 1 day prior to the operation, but PE was deemed unlikely on medical review, and findings on DVT Doppler screening, electrocardiography tracing, and troponin profile were all unremarkable. The patient went on to have surgery without any complications. Preoperatively symptomatic patients were significantly more likely to be harboring preoperative DVTs than asymptomatic patients (p = 0.0181).

**Efficacy of Preoperative Anticoagulation and IVC Filter Insertion in Patients With DVT**

Table 2 shows the time between diagnosis and surgery. The perioperative management protocol for patients with a preoperative DVT is depicted in Fig. 2. All 7 patients with preoperative DVTs were referred to the interventionalist radiologist for the insertion of an IVC filter. Of these patients, 6 underwent tumor resection and/or debulking, and 1 underwent biopsy. The IVC filter was inserted up to 72 hours before the operation took place. In practice, the mean time at which it was inserted in these patients was 44 ± 9.6 hours (SEM) preoperatively.

The management plan consisted of full anticoagulation in all patients prior to surgery, usually with therapeutic-dose enoxaparin, until an IVC filter was inserted. Depending on the timing of the operation, dictated by the type of tumor and urgency of the operation, the period of preoperative anticoagulation was highly variable. In the case of a stable meningioma, the time that patients underwent anticoagulation therapy ranged between 1 and 3 months. Patients with more aggressive tumors underwent anticoagulation therapy for a shorter duration (ranging from 1 to 3 weeks), weighing the risk of further VTE against the risk of tumor progression. In particular, 1 patient who was diagnosed with a glioblastoma did not receive preoperative low-molecular-weight heparin anticoagulation. Because of clinical urgency, this patient underwent surgery 24 hours after her DVT was diagnosed and after an IVC filter was inserted. Anticoagulation was commenced postoperatively as per our protocol.

**Postoperative Anticoagulation**

All patients, both with and without preoperative DVT findings, were started on a regimen of prophylactic-dose enoxaparin usually within 24 hours of surgery, unless there were contraindications, such as an intraoperative hemorrhage. In patients with preoperative DVTs, this dose would then be escalated to treatment-dose enoxaparin if their risk of intracranial hemorrhage was deemed to be sufficiently low, typically at least 1 week after surgery. The exception to this practice was a patient who developed hydrocephalus requiring an external ventricular drain. Of note, with this protocol no patient developed postoperative intracranial hemorrhage.

**Postoperative VTE**

Postoperative scans were only obtained on the grounds of clinical need. The total number of new postoperative DVT/PEs was 2, both occurring in patients with DVTs.

The first patient was diagnosed with a unilateral DVT in the preoperative assessment. An IVC filter was therefore inserted before his successful craniotomy for a very large olfactory groove meningoïma. Because of the large tumor bed, pharmacological anticoagulation was not commenced. Unfortunately, 2 weeks after discharge the patient was readmitted with ventriculitis. He was also noted to have erythema and swelling of both lower limbs. Doppler ultrasonography revealed bilateral DVTs that had progressed from his previous preoperative scan, at which point he had a unilateral DVT. He was managed with intraventricular antibiotics through a drain and initially managed with prophylactic-dose enoxaparin, as full anticoagulation was thought to increase the risk of intracranial hemorrhage in the presence of a ventricular drain. The patient recovered well on this therapy with no further complications.

The second patient was found to have a unilateral DVT during presurgical assessment, which was managed with an IVC filter. He proceeded to undergo an uncomplicated craniotomy for a glioblastoma. Postoperatively, he was started on a regimen of prophylactic-dose enoxaparin. As per our protocol, there was a plan to escalate his treatment to therapeutic-dose enoxaparin; however, 3 weeks after the initial operation, the patient collapsed and was diagnosed with bilateral PEs on CT pulmonary angiography. He was promptly started on a regimen of therapeutic-dose enoxaparin with no further complications.

**Discussion**

Our study demonstrates that routine preoperative DVT screening in neurooncology patients yielded a preoperative DVT-positive rate of 6% (7/115). This is a significant proportion of patients undergoing neurosurgical intervention with VTEs that had been undiagnosed and untreated up to that point, especially as 5 of the 7 patients were asymptomatic for DVT. This rate is higher than that reported in some series of general neurosurgical patients.15
Identification of this risk allows for closer monitoring of this cohort and appropriate management with a period of preoperative anticoagulation and IVC filter insertion to minimize risks of further VTE. Five of the 7 patients with a preoperatively diagnosed DVT did not have any further complications under our treatment regimen. For the 2 patients who did go on to have further VTE (1 PE and 1 bilateral DVT), we felt that the risk of intracranial hemorrhage was too high to initiate full anticoagulation in the postoperative period. Although the identification of preoperative DVT did not fully prevent further VTE here, it avoided mortality and long-term morbidity. Furthermore, there were no additional complications from our treatment protocol of anticoagulation and IVC filter insertion. In addition, the knowledge of preoperative DVT status allowed for closer monitoring of this high-risk group, which might have led to earlier identification of subsequent DVT/PE, allowing prompt treatment and reduced morbidity/mortality. Our study also offers quality assurance in that no patient with a negative preoperative duplex scan of the legs went on to develop DVT/PE during our follow-up period, all receiving prophylactic-dose enoxaparin starting the day after the operation. Furthermore, there were no instances of postoperative intracranial hemorrhage in our patients with this protocol, underpinning its safety.

Patients with symptoms and signs suggestive of DVT preoperatively had a significantly higher risk of DVT on Doppler scanning (p = 0.0181). Clearly, any patient reporting symptoms and a clinical suspicion of VTE should be fully investigated. However, 5 of 7 (71%) of the patients with preoperative DVT did not report symptoms. This further underpins the value of screening in this group. We also note that increased age (p = 0.0321) and previous history of VTE (p = 0.0088) were significant risk factors for the presence of preoperative DVT. These groups of patients also require increased vigilance in monitoring and treating VTE. Of note, a higher CCI, tumor type, or smoking history did not achieve statistical significance as risk factors for VTE.

Our preoperative DVT rate of 6% is consistent with other estimates in the literature, which range from 3% to 23%. However, all estimates indicate that VTE in neurosurgical patients is a significant cause of morbidity. We believe that our treatment protocol presents a valuable method in both diagnosing and treating VTE safely in a group of patients with a high risk of hemorrhage from anticoagulation. Such a treatment protocol may prove useful in other surgical specialties that deal with patient groups who are at high risk for VTE or require surgical intervention, such as hip fracture surgery or major trauma patients, where DVT rates have been estimated to be as high as 50%.

Conclusions

VTE is a significant cause of morbidity and mortality in neurooncology patients. Preoperative screening for DVT is a worthwhile endeavor in patients undergoing neurosurgical intervention. A multidisciplinary approach incorporating expertise in anticoagulation and IVC filter insertion can be safe and minimize further VTE in such patients. This treatment protocol could potentially also be effective for general neurosurgical patients and other surgical specialties in which patients at a high risk of developing VTE require surgical intervention.

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References


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

Supplemental Information
Previous Presentations
Results of the present study were shared during an oral presentation at the Society of British Neurosurgeons Spring Meeting, The Sage, Gateshead, United Kingdom, April 22, 2016.

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