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## Original Paper

# Incidence and Risk of Thromboembolism During Treatment of High-grade Gliomas: a Prospective Study

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**A prospective study of a series of 77 patients on adjuvant radiochemotherapy following surgery for high-grade gliomas was conducted to evaluate the risk of deep vein thrombosis and identify risk factors. We found a 20.8% risk of deep vein thrombosis at 12 months (standard error = 4.8%) and a 31.7% risk (standard error = 7.4%) at 24 months (Kaplan–Meier method). Twenty patients (26%) developed deep vein thrombosis with a maximum incidence within the first 7 months after surgery when chemotherapy was still being administered, often with corticosteroids. The risk factors identified were histology (glioblastoma versus anaplastic astrocytoma, $P = 0.032$, log rank test; 0.0485 L-ratio) and the presence of paresis ($P = 0.010$, log rank test; 0.0161 L-ratio). A borderline tendency was found for an association between the deep vein thrombosis site and the side of paresis ($P = 0.103$, Fisher's exact test). Four patients (5%) had massive pulmonary embolism, which was fatal in 3 (4%).** © **1997 Elsevier Science Ltd.**

**Key words: deep vein thrombosis, high-grade gliomas, prophylaxis, pulmonary embolism**
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## INTRODUCTION

THROMBOEMBOLISM FREQUENTLY occurs in cancer patients and while the aetiology and pathogenesis are not well understood, there are indications that the cancer itself releases substances that trigger the coagulation cascade [1]. This explains the relatively high incidence of thromboemboli in patients undergoing chemotherapy, when neoplastic lysis is provoked.

The incidence of deep vein thrombosis is higher in patients with gynaecological, pancreatic and brain tumours [2]. Occurring in the immediate postoperative period in 29–43% of patients following brain surgery, deep vein thrombosis seems to be due to the release of thromboplastin, which activates the extrinsic coagulation pathway which is mainly contained in the brain [3]. In their study of two groups of patients (one underwent abdominal surgery and the other brain surgery for a primary tumour), Iberti and associates [4] found a significant reduction in partial thromboplastin and bleeding times which, in the latter group, was associated with a rise in coagulation factor IX. In such cases, factor IX values may be high because of fluid restriction due to the administration of osmotic diuretics during surgery with consequent haemoconcentration. These patients have an increase in their haematocrit and osmolality and the increase in haemoconcentration may contribute to the increase in factor IX and other coagulation pro-enzymes serum levels, as well as an increase in one or multiple coagulation factors in the contact activation pathway, leading to shortened partial thromboplastin and bleeding times [5].

The risk factors identified for deep vein thrombosis are advanced age, limb weakness, immobilisation (venous stasis is probably one of the main factors due to absent muscle pump effect as well as venous stagnation in the intra-abdominal organs), varicose veins, heart disease, use of oral contraceptives, previous episodes of deep vein thrombosis, obesity and previous trauma to the legs [6]. The most serious complication from deep vein thrombosis is pulmonary embolism, which is fatal in 20% of cases and the risk of its onset increases with each subsequent episode. Although

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embolisms may originate in any leg vein, most occur in the proximal iliofemoral vessels.

In view of the high incidence of deep vein thrombosis and risk of pulmonary embolism, together with their important sequelae, many neurosurgical centres provide prophylaxis with peri-operative elastic support stockings or tights and intermittent external pneumatic leg compression [7]. Following reports [8] that appear to rule out postoperative intracranial bleeding due to heparin therapy, minidoses of subcutaneous heparin [9] have been administered. This preventive measure appears encouraging: the risk of immediate postoperative deep vein thrombosis has reportedly fallen from 27 to 4.5% [10], and it is now widely accepted that postoperative heparin therapy is indicated in patients who have undergone brain surgery. However, it has yet to be clarified, for how long the therapy should be continued. Some authors have observed a high incidence of deep vein thrombosis and pulmonary embolism throughout the course of the disease, not only during the immediate postoperative period. In fact, among patients with high-grade brain tumours, 8.4% have been found to have pulmonary embolism [11] and 27.5% deep vein thrombosis [12] at autopsy. The aim of this study was to monitor the occurrence of deep vein thrombosis in a group of patients undergoing standard treatment for high-grade glioma in order to verify the trend for the incidence of deep vein thrombosis from a month after surgery to death in the absence of a treatment variable.

## PATIENTS AND METHODS

*Patient selection*

After obtaining their informed consent, we entered patients with high-grade gliomas into this study if they met the following criteria: a histological diagnosis of anaplastic astrocytoma or glioblastoma based on a three-tiered system [13]; age 18–70 years at the time of diagnosis (in view of the potentially greater neurological toxicity of concomitant radio- and chemotherapy, patients over the age of 70 years were not included in the study); Karnofsky performance status (KPS) of at least 50; a life expectancy of over 8 weeks; postoperative computed tomography (CT) scan showing evaluable disease; adequate bone marrow reserve (white blood count >4000 and platelet count >100 000); normal baseline liver (serum bilirubin level <20 mM/l), renal (serum creatinine level <150 mcmol/l), and cardiac function; no previous chemotherapy or radiotherapy and absence of psychiatric disorders.

*Therapeutic protocol*

Seventy-seven patients newly diagnosed were treated with surgery, as extensive as possible, followed by 5000 IU subcutaneous calcium heparin 3 times a day for 20 days. Radiochemotherapy was initiated within 30 days of surgery. All patients received partial brain irradiation to limited fields. The treatment field was determined on a pre-operative CT scan by defining the volume of the contrast-enhancing tumour with a 2 cm margin of apparently normal brain parenchyma. Doses consisted of 1.8–2 Gy/day for 5 days a week, amounting to a total of 59.4 Gy. In the same period, 350 mg/m$^2$ carboplatin was administered on days 1, 22 and 43, and 50 mg/m$^2$ teniposide on days 1, 2, 3, 22, 23, 24, 43, 44 and 45. Subsequently, 200 mg/m$^2$ BCNU was administered, every 8 weeks, for three cycles.

All patients were evaluated by cerebral CT scan at the end of radiotherapy, and after each successive chemotherapy cycle according to Macdonald's criteria [14]. If there was complete remission, therapy was suspended; if remission was partial or disease was stable, therapy was continued until the maximum response was obtained. If disease progression was evident at the end of treatment, therapy was continued with different drugs. Further resection was not routinely considered.

The chemotherapy dose was reduced to 75% on the recycling day if white blood counts or platelet counts were 3500–4000 or 100 000–140 000, respectively, and to 50% if these values were 3000–3500 or 80 000–100 000, respectively.

Supportive treatment consisted of glucocorticoids at doses adjusted according to the patient's clinical condition and the adjusted doses were maintained for the entire duration of radiochemotherapy if the patient's clinical condition allowed it and up to the first CT evaluation. If the dosage was increased because of a marked clinical deterioration, this was recorded when evaluating the response, as described in Macdonald's criteria [14]. Anticonvulsants were used as medically indicated.

Deep vein thrombosis was diagnosed clinically on the basis of the presence of the following symptoms: pain, rubor, swollen, tender, hot calf with venous dilation or a positive Homan's sign. In all patients with one or more of these symptoms, a search was made for the D-dimer fraction and fibrinogen, followed by duplex ultrasonography scan [15]. This diagnostic method does not always reveal deep vein thromboses, but this is the method currently used by us in clinical practice for this type of patient.

Pulmonary embolism was diagnosed clinically (dyspnoea, haemoptysis, pleural chest pain, pleural friction rub, fever, right heart failure or cardiovascular collapse), radiologically (chest X-ray), and by ventilation–perfusion lung scanning performed with $^{99}$Tc-labelled macroaggregated albumin which detects pulmonary blood flow abnormalities associated with pulmonary embolism. If ventilation–perfusion scans in symptomatic patients showed a high or intermediate probability for pulmonary embolism, heparin treatment was initiated and patients with a 'low probability' scan were treated if they presented clinical signs of deep vein thrombosis at ultra sonography.

*Study objectives and endpoints*

Our endpoints were to evaluate the incidence of deep vein thrombosis, observe whether there were correlations with the known risk factors, and establish the time of onset of deep vein thrombosis after starting therapy. The estimated incidence of deep vein thrombosis was calculated using Kaplan–Meier's product limit method [16].

Differences between survivals were tested for statistical significance of various parameters using both the univariate log-rank test [17] and the multivariate L-ratio test [18]. Fisher's exact test was used to evaluate independence in each two-by-two table. All cases were analysed for the following prognostic factors: age; histology; performance status; gender; tumour site; obesity; use of oral contraceptives; hypertension; diabetes; and prior deep vein thrombosis. Patients' age and performance status distributions were dichotomised ($\leq$60 versus >60, and $\leq$70 versus >70, respectively) for univariate log-rank analysis. When the multi-

*Table 1. Risk factors for deep vein thrombosis in patients treated for high-grade gliomas*

| | Deep vein thrombosis | |
|---|---|---|
| | Present | Absent |
| Number of patients | 20 (26%) | 57 (74%) |
| Median age (years) | 54 | 51 |
| Male/female | 10/10 | 26/31 |
| Median performances status | 70 | 80 |
| Histology | | |
| glioblastoma | 19 | 42 |
| anaplastic astrocytoma | 1 | 15 |
| Site of tumour | | |
| right side | 8 (10%) | 24 (31%) |
| left side | 12 (16%) | 33 (43%) |
| Temporal | 9 (12%) | 23 (30%) |
| Frontal | 2 (3%) | 18 (23%) |
| Parietal | 8 (10%) | 15 (19%) |
| Occipital | 1 (1%) | 1 (1%) |
| Risk factors | | |
| obesity | 4 | 7 |
| hypertension | 5 | 11 |
| diabetes | 6 | 5 |
| oral contraceptives | 0 | 3 |
| Previous deep vein thrombosis/pulmonary embolism | 0/0 | 0/0 |

variate L-ratio test was performed, the former variables were analysed as both discrete and continuous.

## RESULTS

*Patient characteristics (Table 1)*

Of the 77 patients (36 men, 41 women; mean age 52 years, range 23–70 years), 61 had glioblastoma and 16 anaplastic astrocytoma. The tumour was on the left side in 45 patients (58%) and on the right in 32 (42%); the tumour site was temporal in 32 cases (42%), parietal in 23 (30%), frontal in 20 (26%) and occipital in 2 (3%).

All patients were available for follow-up from surgery to death. The mean duration of follow-up of all 77 patients was 74.4 weeks; in the 57 patients without deep vein thrombosis (DVT) the follow-up was 78.5 weeks and in the 20 patients with DVT the follow-up was 62.8 weeks. None developed clinical signs of deep vein thrombosis during the postoperative period. This may have been due to the administration of prophylactic subcutaneous calcium heparin for 15 days immediately before surgery. It is, however, possible that some venous thromboses were not identified because of the type of diagnostic evaluation used. None of the patients had endocranial bleeding despite the recent surgery and prophylaxis with subcutaneous calcium heparin. Of our 77 patients, 20 (26%) developed deep vein thrombosis, which was diagnosed clinically and confirmed by duplex ultrasonography (Table 2). The estimated probability of deep vein thrombosis was 20.8% at 12 months (standard error = 4.8%), and 31.7% (standard error = 7.4%) at 24 months (Kaplan–Meier method; Figure 1). Deep vein thrombosis presented on the paretical side in 14 cases (70%). Of the 20 patients, 17 were treated with i.v. heparin, (followed by warfarin in 12 cases, and by subcutaneous calcium heparin in 5 cases); a vena cava filter was also positioned in one of these patients for repeated episodes of thromboembolism during therapy. In the other three cases, treatment was not started because of sudden death from pulmonary embolism. Complete recovery was achieved in 12/20 patients (60%). Eighteen of the 20 patients (90%) had radiological evidence of tumour. Nine (45%) showed a

*Table 2. Characteristics of patients with deep vein thrombosis*

| | |
|---|---|
| Number of patients | 20 (26%) |
| Deep vein thrombosis in paretic leg | 14/20 (70%) |
| Bilateral deep vein thrombosis | 1/20 (5%) |
| Treatment with continuous heparin infusion* | 17/20 (85%) |
| Subsequent treatment | |
| warfarin | 12/17 (71%) |
| heparin s.c. | 5/17 (29%) |
| inferior vena cava filter | 1/17 (6%) |
| Complete recovery | 12/20 (60%) |
| Pulmonary embolism | 4/20 (20%) |
| Time from deep vein thrombosis to death | 8 months |

*There were three sudden deaths from pulmonary embolism: in these cases anticoagulant therapy could not be started—the first patient died while on radiotherapy (60 days after surgery), the second died immediately after radiotherapy (80 days after surgery); and the third died while on chemotherapy (10 months after surgery).

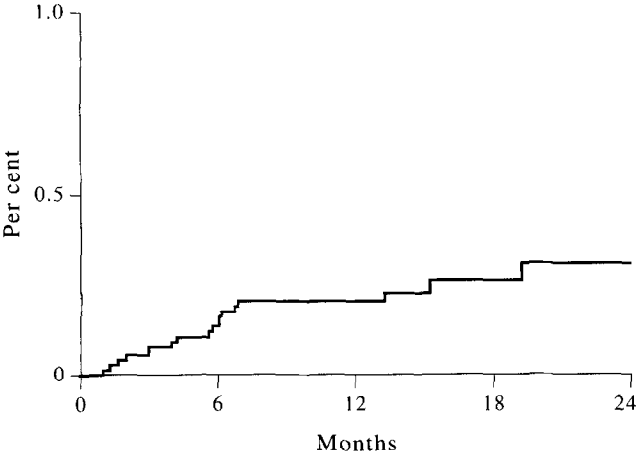


**Figure 1. Estimated incidence of deep vein thrombosis (Kaplan–Meier's product limit method).**

*Table 3. Details of patients who developed paresis*

| | DVT | |
|---|---|---|
| | Present | Absent |
| Number of patients | 14/20 (70%) | 16/57 (28%) |
| Onset of paresis | | |
| Mean | 13.4 weeks | 24.1 weeks |
| Median | 4.4 weeks | 26.0 weeks |
| Duration of paresis | | |
| Mean | 51.1 weeks | 38.5 weeks |
| Median | 46.0 weeks | 26.0 weeks |

partial response; in 4 (20%) disease was stabilised; 4 (20%) had disease progression and 3 (15%) had recurrences.

Four patients had episodes of pulmonary embolism, diagnosed on the basis of clinical symptoms and ventilation–perfusion lung scan, which as mentioned above, was fatal (Table 2) in three cases. In two of these cases, autopsy findings showed deep vein thrombosis that had not been diagnosed, with deep vein iliofemoral thrombosis—one of these patients did not have active disease, the other responded to treatment. The third patient developed pulmonary embolism while under i.v. heparin treatment for prior deep vein thrombosis. In the only patient who survived pulmonary embolism, this complication presented during the course of anticoagulation treatment for deep vein thrombosis and a vena cava filter was, therefore, positioned.

The only variables found to be significant prognostic factors were the presence of paresis ($P = 0.010$ log-rank test and $P = 0.0161$ L-ratio, Table 3) and histology (classified as glioblastoma versus anaplastic astrocytoma. ($P = 0.032$ log-rank and $P = 0.0485$ L-ratio). A border line correlation between the development of deep vein thrombosis at a specific site and the site of paresis was found ($P = 0.103$, Fisher's exact test). The 14 patients with thromboembolism and paresis had motor impairment with a mean duration of three months (range 1–6 months). Importantly, 15/20 deep vein thromboses developed within 7 months following surgery, and 18/20 patients had radiological signs of a tumoral mass.

## DISCUSSION

Our findings show that during the immediate postoperative period, heparin administration effectively reduced the risk of deep vein thrombosis induced by immobilisation and thromboplastic factors released by the tumour. However, the risk of deep vein thrombosis was still high within the first 7 months after surgery, when the patient was still receiving chemotherapy and corticosteroids, although the risk did not return when treatment was suspended. Chemotherapy may, in fact affect thromboembolic phenomena through various mechanisms; reduction of the fibrinolytic potential [19]; direct injury to the endothelial cells caused by the drugs themselves [20] and interaction with the incremental levels of macromolecular multimers of von Willebrand's factor [21]. Moreover, hypercoagulability secondary to steroid treatment may act synergically with chemotherapy, thus precipitating intravascular coagulation [22]. The only risk factors that emerged from our study were the presence of paresis and histological grade. Unlike other authors [23], we found that age was not a risk factor. Despite our attempts to identify the first clinical signs of deep vein thrombosis, 3/77 patients (4%) died of massive pulmonary embolism.

With the administration of anticoagulation prophylaxis in the immediate postoperative period, the risk of deep vein thrombosis has now fallen to 3–5% (determined by $^{125}I$ fibrinogen scanning) [8] and there were no cases in our study. Until recently, anticoagulation treatment was considered potentially dangerous because it was believed to expose patients to the risk of endocranial haemorrhage. Ruff and associates [24] treated 103 of their 381 glioma patients with anticoagulants and found no significant difference between the incidence of endocranial haemorrhage in the treated (1.9%) and that in the untreated (2.2%) group.

If anticoagulant treatment is continued for at least 12 months, comparable results can be obtained. The decision to give this type of treatment to patients with high-grade glioma may be limited to those with glioblastoma and lower limb paresis. Warfarin prophylaxis has been used in breast cancer, but this has a lower incidence of deep vein thrombosis. In their randomised study on patients with metastatic breast cancer, Levine and associates [25] treated 152 patients with low doses of warfarin and 159 with a placebo, and found that thromboembolic complications were reduced from 4.5 to 0.7% in the warfarin treated group [$P = 0.031$]. They also found that 2443 Canadian dollars were saved per 100 patients if patients were treated with warfarin [26] and concluded that the problem of prophylactic therapy for deep vein thrombosis should be discussed with the patient, who should be allowed to decide whether to undergo the inconvenience of daily warfarin administration, laboratory controls and a possible risk of bleeding, against a potential complication that is life-threatening, or requires a long hospital stay and may worsen his/her quality of life.

Low molecular weight heparin is now considered standard therapy in the immediate postoperative period. If it were administered on a long-term basis, it could obviate the inconveniences of treatment with warfarin. Unfortunately, even if this were possible it would be too expensive.

Our study suggests the need for a randomised study in order to establish whether or not prophylactic treatment for deep vein thrombosis should be given to patients with high-grade gliomas, at least for the duration of chemotherapy, and to ascertain whether this would be economically advantageous and, above all, lead to an improvement in the quality of life of patients who have undergone surgery and radiochemotherapy for high-grade glioma.

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