

Current Research in Neurology and Neurosurgery

Research Article

Hemorrhage from Brain Tumors during Anticoagulant Therapy

Francesco Maiuri*, Carmela Peca, Marcello Barbato, Sergio Corvino, Serena Pagano, Giuseppe Teodonna and Giuseppe Mariniello

Department of Neurosciences and Reproductive and Odontostomatological Sciences, Neurosurgical Clinic, University "Federico II", Naples, Italy

***Address for Correspondence:** Francesco Maiuri, Department of Neurosciences and Reproductive and Odontostomatological Sciences, Neurosurgical Clinic, University of Naples, Italy, Tel: +390817462581; E-mail: frmaiuri@unina.it

Received: 14 March 2019; **Accepted:** 04 April 2019; **Published:** 05 April 2019

Citation of this article: Maiuri, F., Peca, C., Barbato, M., Corvino, S., Pagano, S., Teodonna, G., et al. (2019) Hemorrhage from Brain Tumors during Anticoagulant Therapy. *Curr Res Neurol Neurosurg*, 2(1): 030-034.

Copyright: © 2019 Maiuri, F, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Objectives: to define the risk of hemorrhage from brain tumors in patients with and without anticoagulant therapy and the best management of the hemorrhage.

Methods: A series of 335 patients operated on for brain tumors was reviewed. Two groups of patients with (group 1) and without (group 2) anticoagulant therapy were considered. The incidence of symptomatic tumor hemorrhage was studied in both groups. In the overall group of patients with hemorrhage, tumor histology, location of the bleeding, management and outcome were investigated.

Results: The incidence of symptomatic hemorrhage in the overall series was 2.4% (8 cases in 335). Four over 92 patients (4.3%) experienced symptomatic hemorrhage during anticoagulant or antiaggregant treatment versus 4 in 243 (1.6%) with no therapy. The difference was not significant. The incidence of hemorrhage in the various histological groups ranges from 0% to 5%, with no significant difference ($p=0.1366$). The site of hemorrhage was intratumoral in 2 cases, intracerebral in 3, subdural in 2 and both intratumoral and subarachnoid in 1. Seven patients underwent one stage surgery and one patient a two-stage operation. Seven survived after surgery, with neurological deficits in 2 cases, and one died postoperatively for severe bleeding.

Conclusion: The treatment with anticoagulant and antiaggregant drugs does not significantly increase the risk of intracranial hemorrhage in patients with primary and metastatic brain tumors. Although urgent surgery is indicated in the majority of the cases, improving coagulation before tumor resection may be advisable in some cases.

Introduction

Hemorrhage in the context of primary or metastatic brain tumors is not infrequent over the course of the disease, ranging from 1% to 14.6% [1-4]. The incidence is rather variable according to various factors, such as incidental or symptomatic occurrence of the bleeding, tumor histology and management procedures (surgery versus adjuvant treatments).

Many patients with brain tumors receive antiaggregant or anticoagulant therapies for previous vascular cerebral or cardiac diseases or as prophylaxis for venous thromboembolism, a frequent

circumstance in patients with brain tumors [5-7]. Although this therapy is very useful to prevent embolism, it can predispose to bleeding complications and tumor hemorrhage.

This study reports a single center experience of hemorrhage from brain tumors in patients with and without anticoagulant therapy. Its aim is to discuss the risk of hemorrhage during antiaggregant and anticoagulant therapy and the best management of this complication.

Materials and Methods

A surgical series of 335 consecutive patients with intracranial tumors operated on and histologically characterized in our

neurosurgical clinic from 2009 to 2015 were retrospectively reviewed. Only adult patients aged ≥ 18 years with complete clinical, radiological and management data were included.

In the series we have separately considered two groups. Group 1 includes patients undergoing antiaggregant and/or anticoagulant therapy at the moment of the tumor diagnosis and treatment; group 2 includes patients with no therapy. In both groups the tumor histology and the incidence of symptomatic tumor hemorrhage were considered. For the evaluation of the hemorrhage only symptomatic cases were considered; cases with minor bleeding with only evidence at imaging studies or at surgical exploration were excluded. The incidence of symptomatic hemorrhage was investigated in both groups 1 and 2 and according to the tumor histology.

In the overall group of patients with symptomatic hemorrhage, the analysed factors included patient age and sex, tumor histology, type of anticoagulant and antiaggregant therapy, site of the hemorrhage, surgical treatment and outcome.

The data were analyzed by the Fisher exact test. A p value ≤ 0.05 was considered statistically significant. All tests were two sides and carried out with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA).

Results

General epidemiological data

In the overall surgical series, 92 patients (27.5%) (group 1) received antiaggregant or anticoagulant therapy and 243 (72.5%) did not receive it. In group 1, 40 patients (43.5%) were treated by antiaggregant drugs, 19 (20.5%) by oral anticoagulants and 33 (36%) by heparin. Duration of the treatment before the diagnosis of intracranial tumor ranged from 3 months to 5.2 years (average 2.7 years).

The distribution of the histological tumor types in the overall series of patients is summarized in Table 1. Among them, meningiomas (37%), high grade gliomas (23%) and brain metastases (20%) were the more frequent tumor types.

The overall incidence of symptomatic hemorrhage correlated to the brain tumor was 2.4% (8 in 335 patients). When comparing the two groups, the rate of tumor bleeding was 4/92 patients (4.3%) in

group 1 with therapy and 4/243 (1.6%) in group 2 with no therapy, with no significant difference ($p = 0,222$).

The incidence of tumor hemorrhage in the various histological groups ranges from 0% to 5%, with no significant difference ($p = 0.1366$) (Table 1).

Data of patients with tumor hemorrhage

The eight patients with tumor hemorrhage (Table 2) were 5 men and 3 women, with an age ranging from 48 to 75 years (average 64 y). The tumor type was meningioma in 3 cases, high grade glioma in 2, metastatic melanoma in 2 and acoustic schwannoma in one.

Among the 8 patients with hemorrhage, two received therapy with oral anticoagulants (warfarin), one with aspirin and one with heparin, whereas 4 did not receive therapy.

The site of tumor bleeding was within the brain parenchyma surrounding the tumor in 3 patients, within the tumor mass in 2, subdural in two and both intratumoral and subarachnoid in one.

Seven patients underwent one stage operation allowing both the evacuation of the bleeding and the tumor resection. In a patient with right parietal meningioma and frontal subdural hematoma occurring during oral anticoagulant therapy (Figure 1), urgent hematoma evacuation was performed; the tumor was then removed one week later after restoring blood coagulation.

The outcome was as follows. Seven out of the 8 patients survived after surgery. Among them 5 did not experience neurological deficits; one with left cystic acoustic schwannoma and intratumoral and subarachnoid bleeding had residual left facial paresis, and another one with intratumoral hemorrhage from right parietal glioblastoma had postoperative left hemiparesis. One patient with large sudden hemorrhage due to a left temporal metastatic melanoma died five days postoperatively in spite of the urgent surgical procedure.

Discussion

Intracranial hemorrhage is a well known complication in patients with intracranial tumors during anticoagulant treatment. Its incidence is rather variable, from 1.9% [8] to 23% [4] (Table 3). In the study of Yust-Katzetal [9] the overall rate of intracranial hemorrhage in the setting of the anticoagulation was 5.2%. Discrepancy of the data is due to several factors, including definition of hemorrhage, different imaging studies, type of anticoagulant drug, length of monitoring.

Bleeding may occur in intratumoral, intracerebral, subarachnoid and subdural locations. Besides, the spectrum of hemorrhage ranges from small clots found in imaging studies to large hemorrhages with significant mass effect. Thus, the true incidence of symptomatic hemorrhage in patients with intracranial tumors is difficult to be exactly defined.

Most published studies include review articles, case reports, small series of cases or series of patients with anticoagulant drugs and no control group without therapy [10]. We have reviewed 9 published articles that include the group of patients with anticoagulation and the control arm with no therapy (Table 3) [4,8,11-17].

Among the 9 reviewed studies, 5 include gliomas [8,11,14,16,17], 3 brain metastases [4,13,15] and one both primary and metastatic tumors [12]. The anticoagulation was obtained by warfarin [8,11],

Table 1: Incidence of hemorrhage according to the tumor type (335 patients).

Tumor type	N.cases(%)	Cases with symptomatic Tumor hemorrhage	%	Statistical significance
High-grade glioma	76 (23%)	2	2,6%	p >0.99
Low-grade glioma	37(11%)	-	0%	p =0.6
Meningioma	124 (37%)	3	2,4%	p>0.99
Metastasis	67 (20%)	2	3%	p = 0.66
Schwannoma	19(5.5%)	1	5%	p= 0.37
Hemangioblastoma	7(2%)	-	0%	p> 0.99
Ependymoma	5(1.5%)	-	0%	p>0.99
Total	335	8	2,4%	p = 0.1366

Citation: Maiuri, F., Peca, C., Barbato, M., Corvino, S., Pagano, S., Teodonna, G., et al. (2019) Hemorrhage from Brain Tumors during Anticoagulant Therapy. *Curr Res Neurol Neurosurg*, 2(1): 030-034.

heparin [4,12] or both [13-17]. The incidence of hemorrhage in the group of patients with anticoagulation ranged from 0% to 23%. The difference of hemorrhage rate in the two groups was statistically significant only in two studies [16,17]. In our series including tumors

of different histology, both intracerebral and extracerebral, the difference was not significant (4.3% vs 1.6%) (p = 0,222).

The risk of hemorrhage during anticoagulant therapy seems to be different according to the tumor histology. Studies including only

Table 2: Data of patients with intracranial tumors and hemorrhage.

Cases	Age/Sex	Tumor	Anticoagulant/ antiplatelet drug	Site of the hemorrhage	Surgical treatment	Outcome
1	58 M	right frontal anaplastic oligodendroglioma	warfarin	intracerebral	one stage	22 mo. survival
2	69 M	left convexity meningioma (WHO II)	ASA	subdural	one stage	cured
3	66 M	left cystic acoustic schwannoma	clexane 6000 UI	intratumoral + subarachnoid	one stage	cured (post-operative left facial paresis)
4	62 M	right convexity meningioma (WHO II)	warfarin	subdural	two stage (hematoma-tumor)	cured
5	75 F	right parietal glioblastoma	none	intratumoral	one stage	left hemiparesis 14 mo. survival
6	68 F	left temporal metastatic melanoma	none	intracerebral	one stage	dead 5 days postoperatively
7	48 F	left petrous bone meningioma	none	intracerebellar	one stage	cured
8	63 M	left parietal metastatic melanoma	none	intratumoral	one stage	3 mo. survival

Table 3: Data of 9 reported studies of symptomatic brain tumor hemorrhage during anti-coagulant treatment.

Authors/year	Tumor type	Patients with anticoagulation	%of hemorrhage	Patients without anticoagulation	% of hemorrhage	Statistical significance
Ruff and Posner 1983 [8]	glioma	103 (warfarin)	1.9%	264	2.2%	n.s.
Choucair et al. 1987 [11]	glioma	22 (warfarin)	0%	14	0%	n.s.
Olin et al. 1987 [12]	primary and metastatic brain tumors	25 (heparin)	4%	24	0%	n.s.
Schiff and De Angelis 1994 [13]	brain metastases	42 (warfarin and heparin)	7%	10	0%	n.r.
Pan et al 2009 [14]	glioblastoma	25 (warfarin and heparin)	8%	121	0.8%	n.r.
Alvarado et al 2012 [15]	metastatic melanoma	53 (warfarin and heparin)	4%	21	0%	n.s.
Norden et al 2012 [16]	glioma	64 (bevacizumab+ warfarin (13) or heparin (51))	20%	218 (bevacizumab)	1%	p=0.02
Donato et al 2015 [4]	brain metastases	104 (heparin)	21% (at 1 y)	189	19% (at 1 y)	n.s.
Khoury et al 2015 [17]	glioblastoma	97 (warfarin and heparin)	15.5%	76	2.6%	p = 0.05
Present study	various brain tumors	92 (warfarin, heparin, antiplatelets)	4.3%	243	1.6%	n.s.

n.s.= not significant
n.r. = not reported

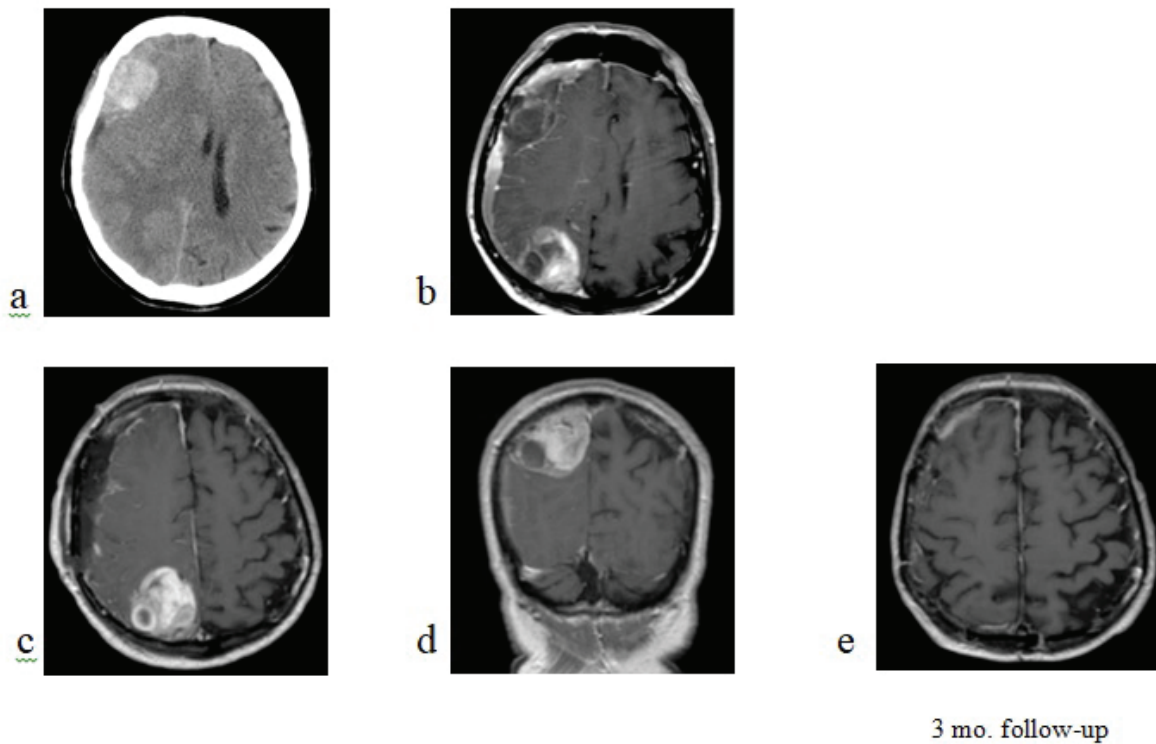


Figure 1: Case 4a. CT scan and b. MRI, post contrast axial T1 sequence, of a 66 y.o. male patient with acute onset of left hemiparesis during anticoagulant therapy with Warfarin: right parietal meningioma with acute frontotemporal subdural bleeding; c - d. MRI, axial and coronal T1 postcontrast sequences seven days after urgent evacuation of the hematoma and withdrawn of the Warfarin: significant decrease of the mass effect due to the hematoma; e. MRI, axial postcontrast sequence after the meningioma resection.

brain metastases [4,13,15] report a rate of hemorrhage between 4% and 21%; in all three studies no significant difference of incidence of hemorrhage between anticoagulation and not anticoagulation groups was evidenced. However, patients with brain metastases from melanoma and renal cell carcinoma have significantly higher risk of hemorrhage during anticoagulant therapy than those harbouring metastases from other primary malignant sites [4,18]. Besides, in a large series, the risk of hemorrhage is not modified by the presence of hypertension, the dose of heparin, the association of aspirin and antiangiogenic agent [4].

Studies including only brain gliomas [8,9,11,14,16,17,19] report a hemorrhage rate between 0 and 20%. The risk of tumor hemorrhage is significantly higher. In fact, the only two studies reporting statistically significant difference between anticoagulation and not anticoagulation groups concern only patients with gliomas [16,17]. There is also evidence that the association of bevacizumab [20,21] and VEGF [17] with the anticoagulation does not increase the risk of developing intracranial hemorrhage.

Thus, malignant gliomas and metastatic melanoma and renal cell carcinoma should be considered at higher risk of hemorrhage during anticoagulant therapy.

In our and other studies the risk of hemorrhage is not different during anticoagulant therapy with heparin versus warfarin [17].

The best management of intracranial hemorrhage from brain tumors during anticoagulant treatments is not well defined and no guidelines exist [18,22,23]. It mainly depends on the bleeding entity and location, the neurological symptoms and signs and the size and type of the tumor. The management decisions must balance the need for surgical decompression and tumor resection and the opportunity of partially restoring the coagulation before resecting the more vascular tumors.

In cases with no or slight symptoms and no significant mass effect, surgery may be delayed for a short time up to improvement of coagulation is obtained; if hemorrhage is the first manifestation of a previously unknown tumor, the radiological diagnosis may also be completed. If the bleeding is conspicuous and results in severe clinical onset (stupor, coma, neurological deficit) and significant mass effect, urgent surgery is necessary. In most cases, mainly with significant intratumoral or intracerebral bleeding, one stage operation may allow to remove both the hematoma and the tumor. However, the resection of large, highly vascularized tumors may be at risk in patients under anticoagulant therapy. In selected patients with significant subdural hematoma and vascularized tumors the blood collection may be evacuated in urgency and the tumor resected after improving the coagulation (Figure 1).

Conclusion

The treatment with anticoagulants does not significantly increase the risk of intracranial hemorrhage in patients with primary brain tumors or brain metastases. The urgent surgery is more often indicated; however, improving the coagulation before resecting more vascularized tumors may be advisable in selected cases.

Limitations of the study

This study is retrospective. Although the overall number of patients included in the analysis is relatively high, the number of cases with hemorrhage is low (2.4%). This is first due to the inclusion of only symptomatic cases; besides, our neurosurgical unit mainly admits patients with intracranial tumors not in emergency, likely resulting in a lower number of cases with associated hemorrhage.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationship, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical Approval

For this retrospective study, no institutional review board approval, or patient consent is required per institutional policy.

References

1. Wakai, S., Yamakawa, K., Manaka, S., Takakura, K. (1982) Spontaneous intracranial hemorrhage caused by brain tumor: its incidence and clinical significance. *Neurosurgery*, 10(4): 437-444.
2. Kondziolka, D., Bernstein, M., Resch, L., Tator, CH., Fleming, JF., Vanderlinden, RG., et al. (1987) Significance of hemorrhage into brain tumors: clinicopathologic study. *J Neurosurg*, 67(6): 852-857.
3. Schrader, B., Barth, H., Lang, EW., Buhl, R., Hugo, HH., Biederer, J., et al. (2000) Spontaneous intracranial haematomas caused by neoplasms. *Acta Neurochir (Wien)*, 142(9): 979-985.
4. Donato, J., Campigotto, F., Uhlmann, EJ., Coletti, E., Neuberger, D., Zwicker, J., et al. (2015) Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood*, 126(4): 494-499.
5. Chan, AT., Atiemo, A., Diran, Lk., Licholai, GP., McLaren Black, P., Creager, MA., et al. (1999) Venous thromboembolism occurs frequently in patients undergoing brain tumor surgery despite prophylaxis. *J Thromb Thrombolysis*, 8(2): 139-142.
6. Chang, SM., Parney, IF., McDermott, M., Barker, FG., Schmidt, MH., Huang, W., et al. (2003) Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. *J Neurosurg*, 98(6): 1175-1181.
7. Wong, JM., Panchmatia, JR., Ziewacz, JE., Bader, AM., Dunn, IF., Laws, ER., et al. (2012) Patterns in neurosurgical adverse events: intracranial neoplasm surgery. *Neurosurg Focus*, 33(5): E16.
8. Ruff, RL., Posner, JB. (1983) Incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol*, 13(3): 334-336.
9. Yust-Katz, S., Mandell, JJ., Wu, J., Yuan, Y., Webre, C., Pawar, TA., et al. (2015) Venous thromboembolism (VTE) and glioblastoma. *J Neurooncol*, 124(1): 87-94.
10. Zwicker, JI., Leaf, RK., Carrier, M. (2016) A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. *J Thromb Haemost*, 14(9): 1736-1740.
11. Choucair, AK., Silver, P., Levin, VA. (1987) Risk of intracranial hemorrhage in glioma patients receiving anticoagulant therapy for venous thromboembolism. *J Neurosurg*, 66(3): 357-358.
12. Olin, JW., Young, JR., Graor, RA., Ruschhaupt, WF., Beven, EG., Bay, JW. (1987) Treatment of deep vein thrombosis and pulmonary emboli in patients with primary and metastatic brain tumors. Anticoagulants or inferior vena cava filter? *Arch Intern Med*, 147(12): 2177-2179.
13. Schiff, D., DeAngelis, LM. (1994) Therapy of venous thromboembolism in patients with brain metastases. *Cancer*, 73(2): 493-498.
14. Pan, E., Tsai, JS., Mitchell, SB. (2009) Retrospective study of venous thromboembolic and intracerebral hemorrhagic events in glioblastoma patients. *Anticancer Res*, 29(10): 4309-4313.
15. Alvarado, G., Noor, R., Bassett, R., Papadopoulos, NE., Kim, KB., Hwu, WJ., et al. (2012) Risk of intracranial hemorrhage with anticoagulation therapy in melanoma patients with brain metastases. *Melanoma Research*, 22(4): 310-315.
16. Norden, AD., Bartolomeo, J., Tanaka, S., Drappatz, J., Ciampa, AS., Doherty, LM., et al. (2012) Safety of concurrent bevacizumab therapy and anticoagulation in glioma patients. *J Neurooncol*, 106(1): 121-125.
17. Khoury, MN., Missios, S., Edwin, N., Sakruti, S., Barnett, G., Stevens, G., et al. (2015) Intracranial hemorrhage in setting of glioblastoma with venous thromboembolism. *Neuro-Oncology Practice*, 3(2): 87-96.
18. Wienstock, MJ., Uhlmann, EJ., Zwicker, JI. (2016) Intracranial hemorrhage in cancer patients treated with anticoagulation. *Thrombosis Research*, S60-65.
19. Altschuler, E., Moosa, H., Selker, RG., Vertosick, FT. (1990) The risk and efficacy of anticoagulant therapy in the treatment of thromboembolic complications in patients with primary malignant brain tumors. *Neurosurg*, 27(1): 74-77.
20. Nghiemphu, PL., Green, RM., Pope, WB., Lai, A., Cloughesy, TF. (2008) Safety of anticoagulation use and bevacizumab in patients with glioma. *Neuro Oncol*, 10(3): 355-360.
21. Seidel, C., Hentschel, B., Simon, M., Schnell, O., Heese, O., Tatagiba, M., et al. (2013) A comprehensive analysis of vascular complications in 3,889 glioma patients from the German Glioma Network. *J Neurol*, 260(3): 847-855.
22. Sjoblom, L., Hardemark, HG., Lindgren, A., Norrving, B., Fahlén, M., Samuelsson, M., et al. (2001) Management and Prognostic Features of Intracerebral Hemorrhage During Anticoagulant Therapy: A Swedish Multicenter Study. *Stroke*, 32(11): 2567-2574.
23. Lyman, GH., Bohlke, K., Khorana, AA., Kunderer, NM., Lee, AY., Arcelus, JI., et al. (2015) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guidelines update. *J Clin Oncol*, 33(6): 654-656.