Journal Pre-proof

Management of patients suffering from hemorrhagic intracranial metastases: Propositions to help the neurosurgeon in emergencies situations based on a literature review

S. Boissonneau MD MSc T. Graillon A. Rolland C. Botella J. Pallud H. Dufour

PII: S0028-3770(20)30469-0

DOI: https://doi.org/doi:10.1016/j.neuchi.2020.11.005

Reference: NEUCHI 1165

To appear in: *Neurochirurgie*

Received Date: 2 February 2018

Revised Date: 9 September 2020

Accepted Date: 14 November 2020

Please cite this article as: Boissonneau S, Graillon T, Rolland A, Botella C, Pallud J, Dufour H, Management of patients suffering from hemorrhagic intracranial metastases: Propositions to help the neurosurgeon in emergencies situations based on a literature review, *Neurochirurgie* (2020), doi: https://doi.org/10.1016/j.neuchi.2020.11.005

Management of patients suffering from hemorrhagic intracranial metastases:

Propositions to help the neurosurgeon in emergencies situations based on a literature review

Boissonneau S.[1,2], Graillon T.[1,3], Rolland A[4], Botella C.[5], Pallud J[5,6], Dufour H.[1,3]

1 - Aix-Marseille Université, APHM, CHU Timone, Department of Neurosurgery, Marseille, France

2- Inserm, INS, Institute of Neurosciences of Systems, Aix Marseille Univ, Marseille, France

3 – Aix-Marseille Université, INSERM, MMG, Marseille, France

4 – Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France

5- Department of Neurosurgery, Centre Hospitalier Saint Anne, Paris, France

6- UMR 1266 INSERM, IMA-BRAIN, Institute of Psychiatry and Neurosciences of Paris, Paris, France

For « la Table ronde des jeunes neurochirurgiens »

For « Le Club de Neuro-oncologie »

Corresponding author:

BOISSONNEAU Sébastien M.D., MSc
Neurosurgery Department – Pr Dufour
La Timone– Assistance Publique Hôpitaux de Marseille
264 Rue Saint-Pierre
13385 Marseille, France
Tel : +334 91 38 55 43
Fax : +334 91 38 42 35
Email : sebastien.boissonneau@ap-hm.fr

ABSTRACT

Introduction:

Brain metastases are the most common intracranial neoplasm in adult patients, and one of the fearsome complications proves to be intratumoral hemorrhage. The neurosurgical management of patients harboring a bleeding brain metastasis is not fully established and there is still today an ongoing debate on the optimal management of these patients. The aim of this article is to provide the neurosurgeons with practical tools to assist in their decision-making process in the management of BMs.

Methods:

We conducted a literature review of the relevant Pubmed, Cochrane, and Google scholar-indexed articles published between 2000 and 2019. The following keywords were entered in the Pubmed search engine: [metastasis], [metastases], [brain metastases], [brain metastasis], [hemorrhage], [hematoma], [blood clot], [intracerebral hemorrhage], [intracranial hemorrhage]. The review was performed in accordance with the PRISMA recommendations.

Results:

Based on PubMed, Cochrane, and Google scholar, 459 articles were retained, 392 were then removed because of their non-adequacy with the topic and, 9 articles were removed because they were not written in English language. So, 58 articles were analyzed. Radiological evaluation is crucial, but few traps exist. The frequency of overall brain tumor-related with intracranial hematoma is 7.2%, with a higher frequency for secondary tumors.

The local recurrence rate after resection of a hemorrhagic metastasis seems to be better probably because of an easier "*en bloc*" resection thanks to the hematoma.

An atypical presentation is reported in up to 4% in patients with chronic or acute *subdural hematoma*. Patients with subarachnoid hemorrhage and epidural hematoma are rare.

A clear-cut correlation between the incidence of bleeding event in brain mets and prior stereotactic radiosurgery was not established

Conclusion:

The current literature pertaining to the neurosurgical management of acute bleeding in brain metastasis is scant and the level of evidence remains low (experts 'opinions; class C). Herein we suggest a flowchart to assist in dealing with those difficult patients.

Introduction

Brain metastases are the most common intracranial neoplasms in adult patients. They appear in 10 to 30% of patient with systemic cancer [1]. Hemorrhagic transformation leads most of the time to a decision that needs to be taken acutely, in an emergency setting and that is consequently not based in the multidisciplinary environment of the tumoral board. The frequency of spontaneous intracerebral hemorrhage in patients with intracranial neoplasms ranges between 1.4 to 10% (average 2.5%) [2–5]. Intracerebral hemorrhage is more frequent in patients with cerebral metastases than in patients with gliomas (14% versus 0.8%, respectively) [6]. Brain metastases from melanoma, renal cell carcinoma, choriocarcinoma, and thyroid carcinoma have a well-known propensity for spontaneous hemorrhage [7]. A dramatic dreadful complication of an intracranial bleeding is the subsequent neurological and functional alteration that may strongly impact the quality of life (QoL) of the patient. The patient's QoL is indeed a crucial criterion to take into account before any neurosurgical procedures and to be weighted up against the functional prognosis and the potentially short overall survival expectancy for patients with brain metastases [8].

Based on the literature review, we herein summarize the epidemiology, clinical features, diagnostic evaluation, neurosurgical management and prognosis for adult patients harboring a brain metastasis-related intracerebral hemorrhage. The goal of this study is to come up with a few suggestions to help the neurosurgeon in their decision-making process in emergency settings.

Methods

A literature search was conducted on PubMed, Cochrane, and Google Scholar in 2019 to identify all studies, except pediatric studies, concerning brain metastases and intracerebral hemorrhage in the English language. The inclusive search dates were from 2000 through 2019 and specific search terms included [metastasis], [metastases], [brain metastases], [brain metastasis], [hemorrhage], [hematoma], [blood clot], [intracerebral hemorrhage], [intracranial hemorrhage]. After the searches were completed, the abstract of each publication was reviewed to determine relevance or adequacy with our topic and selected studies were further analyzed for this review. We used the right reporting tool for practice guidelines in health care to strengthen the methodology [9]. The review was conducted in accordance with PRISMA recommendations [10].

Results

A total of 455 articles in PubMed, 5 in Cochrane and 3 in Google Scholar were initially found with the above-mentioned search criteria. Of those 459 articles were retained after removing duplicates. 392 were then removed because of their non-adequacy with the topic of this article. Indeed, 9 articles were removed because they were not written in English language. So, 58 articles were analyzed and could serve as a basis to establish guidelines.

Currently, there are no surgical guidelines about the surgical management of brain hemorrhagic metastases. In the light of current guidelines for spontaneous stroke hematomas, we advocate an early decompression surgery (clot removal together with metastasis removal) to diminish mass effect, for patient with neurological deterioration and/or vigilance alteration [11,12]. The need of a decompressive craniectomy associated with clot removal is still discussed with conflicting results in few non-randomized trials [13,14]. In the randomized study STICH II,pertaining to patient suffering from an intracerebral hematoma, the authors do not report any increase of disability after surgical clot removing (Class III, Level of evidence B) [11], .The European Stroke Organization (ESO) guidelines for the management of spontaneous intracerebral hemorrhage, favor an early surgery for patients with a Glasgow Coma Scale score 9-12 (Class II, Level of evidence A)[12]. In our review, the results of STITCH II study can't be extrapolated to patients with brain metastases, and the timing for surgery is still controversial. Indeed, these studies seem to be harmful for ultra-early clot removal (< 2 hours) for cerebral hematomas, because it could increase the risk of early re-bleeding (Class III, Level of evidence B). In the opposite, patients with cerebellar hematomas and with a brainstem compression, or a neurologically deterioration, and/or a hydrocephalus should benefit from an ultra-early surgical removal (Class I, Level of evidence B) [15]. This reflection seems to be coherent with the current literature. The removal of hematoma in patient suffering from a neurological deterioration, should be performed. This removal could improve the onco-functional imbalance and avoid death but needs to be analyzed in the light of the oncological prognosis of the patient, with the consequences of the

surgery. This is the reason why we cannot extrapolate the results of STITCH II study with these patients.

Pitfalls

A common diagnostic pitfall is the spontaneous intracranial hematoma (not directly related to a brain metastasis) caused by the systemic neoplasm. Shrader et al. reported in a prospective study of 2041 patients, that the frequency of tumor related with spontaneous intracranial hematoma is 7.2%, with a higher frequency for brain metastases. This point is pivotal for the daily management of patients with spontaneous intracranial hematoma, where a neoplastic disease should be searched for, even in patients with no past medical history of cancer [3,16].

Collision-Tumors

In the literature, exceptional cases reports were reported. Indeed, hemorrhagic brain metastases could also mimic a cavernous angioma. Such an atypical presentation was reported by Lu et al. in two cases of patients with metastatic melanoma [17]. Another kind of vascular brain abnormality is described in the literature. An association of a brain arteriovenous malformation with an intracranial metastasis is reported by Morollon et al. [18], but also in the case of a brain arteriovenous fistulae [19].

Atypical cases

Moreover, neoplastic cranial aneurysm is a rare entity, and according to the primary tumor the risk of bleeding may prove not negligible and is higher than 80% for the vast majority of neoplasms. Neoplastic cranial aneurysms could rupture and bleed more frequently in the case of lung cancer, and a choriocarcinoma rather than a cardiac myxoma [20].
Hemorrhagic brain metastases could show many kinds of imaging presentations. Indeed, Seki et al. reported in 2016 on one patient with dural metastasis mimicking a meningioma [21].

In rare cases, atypical presentation is chronic or acute *subdural hematoma*. This rate is around 0.5 to 4% in these patients [22,23]. Another atypical presentation, was *epidural hematoma* in a patient with a skull metastasis from an ovarian cancer [24].

Another pitfall lies in the risk of patients who are diagnosed with subdural hematoma in the setting of a known cancer. Those patients could have a hemorrhagic dural metastasis misdiagnosed as a subdural hematoma. In case of leukemia or hemopathy, the subdural hematoma can be independent of the bleeding diathesis induced by the disease. This invasion of the dura-mater should lead to perform a dural biopsy during the surgical procedure of the hematoma evacuation [22,25].

Hirooka et al. reported a rare case of a patient with a subarachnoid hemorrhage who developed secondarily, a brain metastasis. Metastases from lung cancer represent the majority of brain metastases [26], and malignant pleural mesothelioma, is a fatal neoplasm, but uncommon. This disease is a consequence of asbestos exposure for many years (more than 40 years). In this rare case, the authors hypothesize that subarachnoid hemorrhage would have led to a blood brain barrier disruption, and *in fine* permitted the development of a brain metastases [20,26].

Another atypical case revelation is during a long air travel: According to the authors the vasoactive factors could be modified by the pressure during a long airplane flight and led to a hemorrhage [27].

Radiosurgery

Cases of fatal bleeding occurring just after, or during radiosurgery for brain metastases have been described but seemed to be truly exceptional and seems to be multifactorial, but there has not been to date compelling evidence of a clear association [28,29]. Few risk factors of delayed bleeding seem to be associated like a peri-tumoral minor oozing of blood before radiosurgery, the use of anticoagulant drug, the use of antiangiogenic drug, and the hemorrhagic predisposition of the primitive neoplasms (melanoma, renal neoplasm) [30].

Neurosurgical management: Propositions

In the light of these element we propose a flowchart to help the neurosurgeon in their decision-making process in acute settings. (Figure 2). We hope that these propositions may improve the complex management of these patients:

Patients without a clear oncological past medical history should systematically benefit from of a pathological analysis of the clot which was removed in emergencies.

Patients with a clear oncological history and a life expectancy superior to 3 months, should have a skull bone biopsy in case of epidural hematoma. A dura-mater biopsy should be done in case of subdural hematoma, and "*en bloc*" resection should be done as much as possible, thanks to the surgical dissection plane to be found around the hematoma.

Patients with a life expectancy of less than 3 months should be oriented for best supportive care (Figure2).

Discussion

Little is known in the literature about the management and the outcomes of patients with hemorrhagic brain metastases. And coagulation status in cancer patients can be altered by different factors:

- Chemotherapy or bone marrow invasion could induce thrombocytopenia [31].

- The coagulation factors may be affected by liver metastases [32,33].
- Targeted therapies, especially tyrosine-kinase inhibitors, seem to increase the frequency of fatal intracranial hemorrhage in patients with brain metastases [34,35].
- Inhibitors of angiogenesis, like bevacizumab (frequently used in renal cancer), which is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), could induce coagulopathy and increase the risk of hemorrhage [36] .The risk of spontaneous tumor hemorrhage related to Bevacizumab administration is still an unsolved issue but seems to be very low in clinical trials [37–39].

Moreover, cancer is a global disease with many consequences on the immune system, with systemic inflammatory response [40] which leads to a kind of hyper-metabolism for the patient and should not be viewed as a single focal lesion for the patient,. This is the reason why patients under anticoagulation therapy, like anti-vitamin K (AVK), or low molecular weight heparin, could have an increased risk of hemorrhage [41].

The survival prognosis of the systemic cancer and the functional prognosis have to be discussed with the referring oncologist, the medical team, and the patient's family. For example, patients suffering from melanoma with brain metastasis who have genetic mutation of BRAF V600E, have a better survival prognosis and should benefit from a more aggressive therapeutic management [42–46] . The genomic heterogeneity of brain metastases, and the molecular profile could be an opportunity for specific therapies [47,48] to improve outcomes and reduce morbidity [49].

Obviously, patients with only few weeks/days of life expectancy should be managed conservatively and benefit from palliative care. The QoL, and particularly the quality of the "last years of life" should remain a key element for the neurosurgeon and the medical oncologists.

Only one study reports the surgical outcomes of hemorrhagic brain metastases. Yoo et al, reported a retrospective series of 21 patients with hemorrhagic metastases (single metastasis in 15 cases, oligo-metastatic condition in 6 cases) with a mean time to progression of 20.8 months and with a median survival time of 11.7 months after surgery. An interesting point is the fact that, the local recurrence after resection of a hemorrhagic metastasis is low: 12 month-free survival is higher than 80% in this series. The progression-free survival reported in the Yoo's paper, seems to be associated with an "*en bloc*" resection [50] (Class II, Level of evidence C).

The functional prognosis should be taken into consideration by neurosurgeons before going for surgery in a patient with brain hemorrhagic metastases. The functional anatomy of human brain white matter pathway should be incorporated in the choice of the surgical approach in order to perform a minimal cortectomy and to gain access to the brain metastases and the clot

through an intra-parenchymal "safe" corridor. The shortest pathway through the brain to the clot is not always the best option as it may disrupt main eloquent subcortical pathways [51]. Indeed, patients with a glioblastoma seems to be more at risk of developing a brain hemorrhage than patients with brain metastases, according to Zwicker et al. [52]. Moreover, anticoagulation use seems to be quite safe for low molecular weight heparin and Oral Factor Xa Inhibitor [53,54].

Conclusion

The current literature pertaining to the neurosurgical management of acute bleeding in brain metastasis is scant and the level of evidence remains low (experts 'opinions; class C) we suggest a flowchart to assist in dealing with those difficult patients [55].

In line with the literature, it appears the benefit of removing hemorrhagic BM really exist when the neurological condition of the patient acutely deteriorates. In the setting of an intracranial bleeding, the possibility of an underlying secondary tumor should be investigated regardless of the existence of an oncological past medical history or not. Multidisciplinary team management of those patients, performed in close interaction with medical oncologists is pivotal to the optimal care in the era of personalized medicine

References

[1] Brastianos PK, Curry WT, Oh KS. Clinical Discussion and Review of the Management of Brain Metastases. J Natl Compr Canc Netw 2013;11:1153–64. https://doi.org/10.6004/jnccn.2013.0133.

[2] Kondziolka D, Bernstein M, Resch L, Tator CH, Fleming JFR, Vanderlinden RG, et al. Significance of hemorrhage into brain tumors: clinicopathological study. Journal of Neurosurgery 1987;67:852–7. https://doi.org/10.3171/jns.1987.67.6.0852.

[3] Schrader B, Barth H, Lang EW, Buhl R, Hugo HH, Biederer J, et al. Spontaneous Intracranial Haematomas Caused by Neoplasms. Acta Neurochirurgica 2000;142:979–85. https://doi.org/10.1007/s007010070052.

[4] Wakai S, Yamakawa K, Manaka S, Takakura K. Spontaneous Intracranial Hemorrhage Caused by Brain Tumor. Neurosurgery 1982;10:437–44. https://doi.org/10.1227/00006123-198204000-00004.

[5] Fewel ME, Thompson BG, Hoff JT. Spontaneous intracerebral hemorrhage: a review. Neurosurg Focus 2003;15:E1.

[6] Maiuri F, D'Andrea F, Gallicchio B, Carandente M. Intracranial hemorrhages in metastatic brain tumors. J Neurosurg Sci 1985;29:37–41.

[7] Kim DG, Lunsford LD, editors. Current and Future Management of Brain Metastasis. vol. 25. S. Karger AG; 2012. https://doi.org/10.1159/isbn.978-3-8055-9618-3.

[8] Stelzer KJ. Epidemiology and prognosis of brain metastases. Surg Neurol Int 2013;4:S192-202.

https://doi.org/10.4103/2152-7806.111296.

[9] Chen Y, Yang K, Marušic A, Qaseem A, Meerpohl JJ, Flottorp S, et al. A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. Ann Intern Med 2017;166:128–32. https://doi.org/10.7326/M16-1565.

[10] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. International Journal of Surgery 2010;8:336–41. https://doi.org/10.1016/j.ijsu.2010.02.007.

[11] Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet 2013;382:397–408. https://doi.org/10.1016/S0140-6736(13)60986-1.

[12] Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 2014;9:840–55. https://doi.org/10.1111/ijs.12309.

[13] Ma L, Liu W-G, Sheng H-S, Fan J, Hu W-W, Chen J-S. Decompressive craniectomy in addition to hematoma evacuation improves mortality of patients with spontaneous basal ganglia hemorrhage. J Stroke Cerebrovasc Dis 2010;19:294–8. https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.07.002.

[14] Shimamura N, Munakata A, Naraoka M, Nakano T, Ohkuma H. Decompressive hemi-craniectomy is not necessary to rescue supratentorial hypertensive intracerebral hemorrhage patients: consecutive single-center experience. Acta Neurochir Suppl 2011;111:415–9. https://doi.org/10.1007/978-3-7091-0693-8_71.

[15] Morgenstern LB, Hemphill JC, Anderson C, Becker K, Broderick JP, Connolly ES, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108–29. https://doi.org/10.1161/STR.0b013e3181ec611b.

[16] Nawabi J, Hanning U, Broocks G, Schön G, Schneider T, Fiehler J, et al. Neoplastic and Non-Neoplastic Causes of Acute Intracerebral Hemorrhage on CT: The Diagnostic Value of Perihematomal Edema. Clin Neuroradiol 2019. https://doi.org/10.1007/s00062-019-00774-4.

[17] Lu AY, Patel AR, Kuzmik GA, Atsina K-K, Bronen RA, Jabbour PM, et al. Brainstem melanomas presenting as a cavernous malformation. Neurochirurgie 2014;60:184–7. https://doi.org/10.1016/j.neuchi.2014.02.005.

[18] Morollón N, Arrese I, Zamora T, Sarabia R. Histology of a cerebral hemorrhage: AVM as a seat of a metastatic choriocarcinoma. Neurocirugia (Astur) 2015;26:143–6. https://doi.org/10.1016/j.neucir.2014.08.001.

[19] Fadli M, Lmejjati M, Amarti A, El Hassani MR, El Abbadi N, Bellakhdar F. [Metastatic and hemorrhagic brain arteriovenous fistulae due to a choriocarcinoma. Case report]. Neurochirurgie 2002;48:39–43.

[20] Zheng J, Zhang J. Neoplastic cerebral aneurysm from metastatic tumor: a systematic review of clinical and treatment characteristics. Clin Neurol Neurosurg 2015;128:107–11. https://doi.org/10.1016/j.clineuro.2014.11.010.

[21] Seki S, Kamide T, Tamase A, Mori K, Yanagimoto K, Nomura M. Intraparenchymal hemorrhage from dural metastasis of breast cancer mimicking meningioma. Neuroradiol J 2016;29:179–82. https://doi.org/10.1177/1971400916638351.

[22] Tseng S-H, Liao C-C, Lin S-M, Chen Y, Shun C-T. Dural metastasis in patients with malignant neoplasm and chronic subdural hematoma. Acta Neurol Scand 2003;108:43–6. https://doi.org/10.1034/j.1600-0404.2003.00080.x.

[23] Prasad BC, Chandra VVR, Varaprasad G. Dural metastases in chronic myeloid leukemia presenting as subdural hematoma. Turk Neurosurg 2012;22:777–8. https://doi.org/10.5137/1019-5149.JTN.4050-10.2.

[24] Kumar PM, Manisha M. Epidural hematoma secondary to solitary skull metastasis from an ovarian carcinoma. Asian J Neurosurg 2014;9:112–4. https://doi.org/10.4103/1793-5482.136729.

[25] Chye C-L, Lin K-H, Ou C-H, Sun C-K, Chang I-W, Liang C-L. Acute spontaneous subdural hematoma caused by skull metastasis of hepatocellular carcinoma: case report. BMC Surg 2015;15:60. https://doi.org/10.1186/s12893-015-0045-x.

[26] Hirooka A, Tamiya A, Kanazu M, Nonaka J, Yonezawa T, Asami K, et al. Brain Metastasis of Pleural Mesothelioma after a Subarachnoid Hemorrhage. Intern Med 2016;55:779–81. https://doi.org/10.2169/internalmedicine.55.3765.

[27] Goldberg CR, Hirschfeld A. Hemorrhage within brain tumors in association with long air travel. Acta Neurochir (Wien) 2002;144:289–93. https://doi.org/10.1007/s007010200038.

[28] Redmond AJ, Diluna ML, Hebert R, Moliterno JA, Desai R, Knisely JPS, et al. Gamma Knife surgery for the treatment of melanoma metastases: the effect of intratumoral hemorrhage on survival. J Neurosurg 2008;109 Suppl:99–105. https://doi.org/10.3171/JNS/2008/109/12/S16.

[29] Yomo S, Hayashi M. Fatal tumoral hemorrhage after stereotactic radiosurgery for metastatic brain tumors: report of three cases and review of literature. Acta Neurochir (Wien) 2012;154:1685–90. https://doi.org/10.1007/s00701-012-1447-5.

[30] Wowra B, Siebels M, Muacevic A, Kreth FW, Mack A, Hofstetter A. Repeated gamma knife surgery for multiple brain metastases from renal cell carcinoma. J Neurosurg 2002;97:785–93. https://doi.org/10.3171/jns.2002.97.4.0785.

[31] Ten Berg MJ, van den Bemt PMLA, Shantakumar S, Bennett D, Voest EE, Huisman A, et al. Thrombocytopenia in adult cancer patients receiving cytotoxic chemotherapy: results from a retrospective hospital-based cohort study. Drug Saf 2011;34:1151–60. https://doi.org/10.2165/11594310-000000000-00000.

[32] Campagna M-C. Chemotherapy Complications. Hospital Medicine Clinics 2016;5:400–12. https://doi.org/10.1016/j.ehmc.2016.02.001.

[33] Duwe G, Knitter S, Pesthy S, Beierle AS, Bahra M, Schmelzle M, et al. Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. Eur J Surg Oncol 2017;43:1668–81. https://doi.org/10.1016/j.ejso.2017.05.008.

[34] Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006;24:25–35. https://doi.org/10.1200/JCO.2005.02.2194.

[35] Pouessel D, Culine S. High Frequency of Intracerebral Hemorrhage in Metastatic Renal Carcinoma Patients with Brain Metastases Treated with Tyrosine Kinase Inhibitors Targeting the Vascular Endothelial Growth Factor Receptor. European Urology 2008;53:376–81. https://doi.org/10.1016/j.eururo.2007.08.053.

[36] Elice F, Rodeghiero F. Side effects of anti-angiogenic drugs. Thrombosis Research 2012;129:S50–3. https://doi.org/10.1016/S0049-3848(12)70016-6.

[37] Carden CP, Larkin JMG, Rosenthal MA. What is the risk of intracranial bleeding during anti-VEGF therapy? Neuro-Oncology 2008;10:624–30. https://doi.org/10.1215/15228517-2008-010.

[38] Besse B, Lasserre SF, Compton P, Huang J, Augustus S, Rohr U-P. Bevacizumab safety in patients with central nervous system metastases. Clin Cancer Res 2010;16:269–78. https://doi.org/10.1158/1078-0432.CCR-09-2439.

[39] Wang Z, Yang J-J, Tu H-Y, Yan H-H, Wu Y-L. Retrospective study on bevacizumab in the treatment of non-small cell lung cancer with brain metastases. Int J Clin Oncol 2020;25:267–73. https://doi.org/10.1007/s10147-019-01552-5.

[40] Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011;144:646–74. https://doi.org/10.1016/j.cell.2011.02.013.

[41] Akl EA, Kahale L, Barba M, Neumann I, Labedi N, Terrenato I, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2014:CD006650. https://doi.org/10.1002/14651858.CD006650.pub4.

[42] Chapman CH, Zhu T, Nazem-Zadeh M, Tao Y, Buchtel HA, Tsien CI, et al. Diffusion tensor imaging predicts cognitive function change following partial brain radiotherapy for low-grade and benign tumors. Radiother Oncol 2016;120:234–40. https://doi.org/10.1016/j.radonc.2016.06.021.

[43] Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–14. https://doi.org/10.1056/NEJMoa1203421.

[44] Carron R, Gaudy-Marqueste C, Amatore F, Padovani L, Malissen N, Balossier A, et al. Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: A retrospective study of safety and efficacy. Eur J Cancer 2020;135:52–61. https://doi.org/10.1016/j.ejca.2020.04.028.

[45] Gaudy-Marqueste C, Dussouil AS, Carron R, Troin L, Malissen N, Loundou A, et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. Eur J Cancer 2017;84:44–54. https://doi.org/10.1016/j.ejca.2017.07.017.

[46] Gaudy-Marqueste C, Carron R, Delsanti C, Loundou A, Monestier S, Archier E, et al. On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases. Annals of Oncology 2014;25:2086–91. https://doi.org/10.1093/annonc/mdu266.

[47] Dagogo-Jack I, Carter SL, Brastianos PK. Brain Metastasis: Clinical Implications of Branched Evolution. Trends Cancer 2016;2:332–7. https://doi.org/10.1016/j.trecan.2016.06.005.

[48] Shonka N, Venur VA, Ahluwalia MS. Targeted Treatment of Brain Metastases. Curr Neurol Neurosci Rep 2017;17:37. https://doi.org/10.1007/s11910-017-0741-2.

[49] Preusser M, Capper D, Ilhan-Mutlu A, Berghoff AS, Birner P, Bartsch R, et al. Brain metastases: pathobiology and emerging targeted therapies. Acta Neuropathol 2012;123:205–22. https://doi.org/10.1007/s00401-011-0933-9.

[50] Yoo H, Jung E, Gwak HS, Shin SH, Lee SH. Surgical Outcomes of Hemorrhagic Metastatic Brain Tumors. Cancer Res Treat 2011;43:102–7. https://doi.org/10.4143/crt.2011.43.2.102.

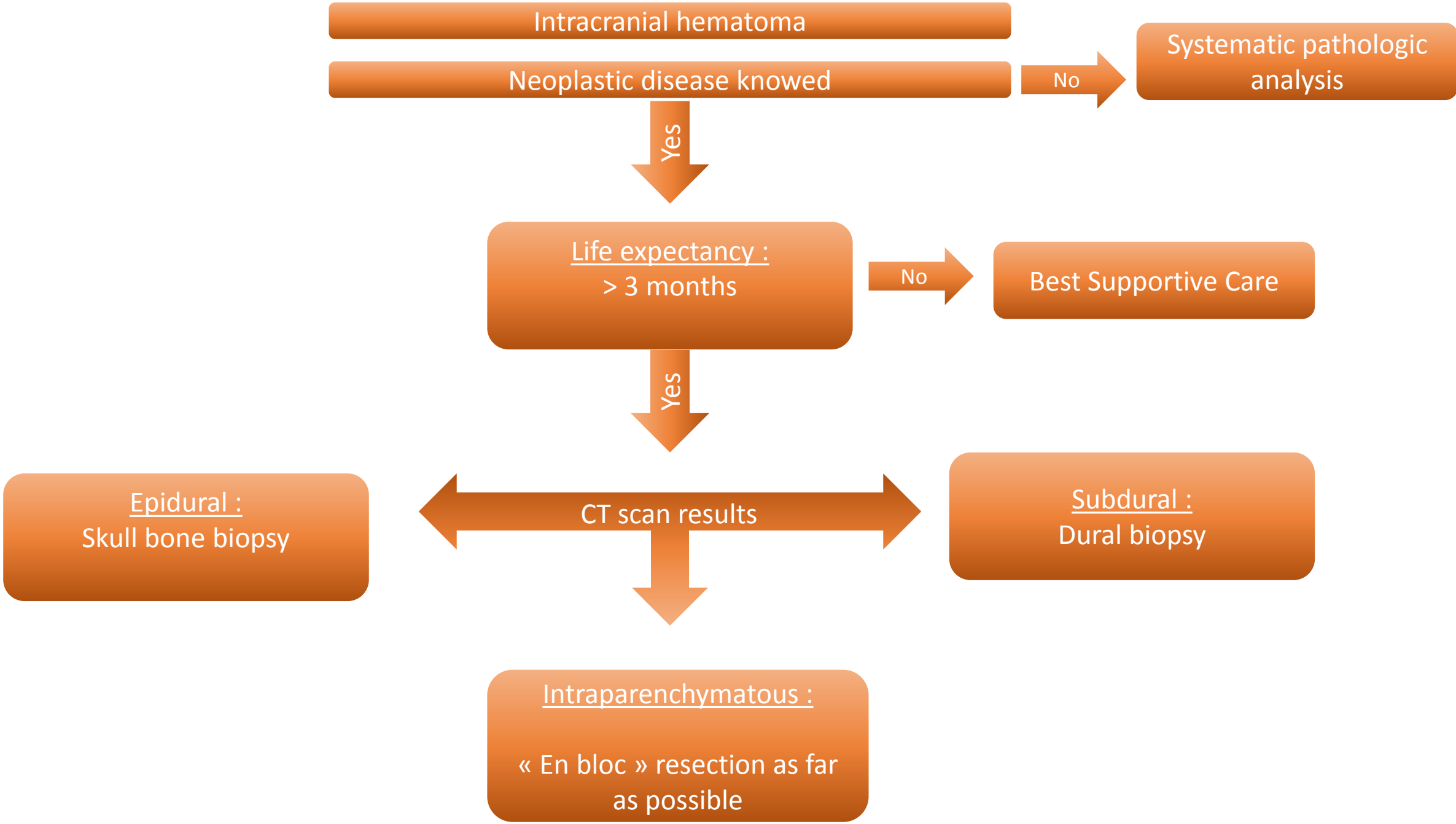
[51] Voets NL, Bartsch A, Plaha P. Brain white matter fibre tracts: a review of functional neuro-oncological relevance. J Neurol Neurosurg Psychiatry 2017;88:1017–25. https://doi.org/10.1136/jnnp-2017-316170.

[52] Zwicker JI, Karp Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. J Thromb Haemost 2016;14:1736–40. https://doi.org/10.1111/jth.13387.

[53] Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). JCO 2018;36:2017–23. https://doi.org/10.1200/JCO.2018.78.8034.

[54] Klerk CPW, Smorenburg SM, Otten H-M, Lensing AWA, Prins MH, Piovella F, et al. The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy. JCO 2005;23:2130–5. https://doi.org/10.1200/JCO.2005.03.134.

[55] Abettan C. Between hype and hope: What is really at stake with personalized medicine? Med Health Care Philos 2016;19:423–30. https://doi.org/10.1007/s11019-016-9697-2.


Intracranial hematoma
Neoplastic disease knowed
No
Systematic pathologic analysis
Yes
Life expectancy :
> 3 months
No
Best Supportive Care
Yes
Epidural :
Skull bone biopsy
CT scan results
Subdural :
Dural biopsy
Intraparenchymatous :
« En bloc » resection as far as possible