UNIVERSITÀ DEGLI STUDI FIRENZE

DOTTORATO DI RICERCA IN Scienze Cliniche (Medicina Clinica e Sperimentale)

CICLO XXII

COORDINATORE Prof. Matucci Cerinic

COMPUTED TOMOGRAPHY FOR EVALUATION OF TUMOUR ANGIOGENESIS: THE CONTRIBUTION OF ADVANCED QUANTITATIVES PARAMETERS.

Settore Scientifico Disciplinare MED/41

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ABSTRACT

Objective.

The aim of this study was to know if quantitative parameters of perfusion CT could predict the response of bevacizumab therapy on patients with brain cancer based on the RECIST.1.1 guidelines

Material and methods.

This study included 18 patients (11 men and 7 women; mean age, 47,11 years) with brain neoplasm who were undergoing bevacizumab treatment. by comparing baseline studies with the best response achieved after completion of bevacizumab treatment and chemotherapy, patients were divided into two groups according to RECIST (version 1.1) guidelines as follows; responders (CR or PR) and non-responders (SD or PD). CT perfusion parameters (blood flow, blood volume, mean transit time, and permeability) were performed on baseline and were correlated with tumor size at first, then a logistic regression model was used to evaluate predictive factors for a response to bevacizumab treatment.

Results.

There were early changes shown after only few week of bevacizumab therapy between the 9 responders group of patients and the remaining 9 no responders patients. Clinical responders showed significantly higher blood flow (P=0.01) than non-responders. Blood flow, accuracy was 80.2% for detection of clinical responders when the cut-off point was set at 50 ml/100 g/min. Patients with high blood flow tumors (≥50 ml/100 g/min) survived significantly longer than those with low blood flow tumors (<50 ml/100 g/min) (p=0.007).

Multivariate analysis identified blood flow as a significant independent prognostic factor (p = 0.006; risk ratio, 5.18; 95% IC, 0.48-22.68).

Conclusion.

This study has shown the possibility that Perfusion CT could predict the response to BV treatment in brain tumor.

Keywords: bevacizumab, Perfusion CT, angiogenesis, brain tumor

THESIS TITLE:

COMPUTED TOMOGRAPHY FOR EVALUATION OF TUMOR ANGIOGENESIS: THE CONTRIBUTION OF ADVANCED QUANTITATIVE PARAMETERS.

By YEO DOGNIMIN OUSMANE, Md

ACKNOWLEDGEMENT.

A very special Thank You to my supervisor**, Prof Lorenzo Livi**

Thanks also to my family and friends.

ABBREVIATIONS

BV: BEVACIZUMAB
WHO: World Health Organization
CT: Computed Tomography
MRI: Magnetic Resonance Imaging
PCT: Perfusion Computed Tomography
CBV: Cerebral Blood Volume
CBF: Cerebral Blood Flow
MTT: Mean Transit Time
PET/CT: Proton Emission Tomography CT
ACA: Anterior Cerebral Artery
MCA: Middle Cerebral Artery
CR : Complete Response
PR : Partial Response
SD: Stable Disease
PD: Progressive Disease

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INTRODUCTION [1,2,3]

According to the WHO World Cancer Report 2000, cancers tend to become a major public health problem in developing countries. Brain tumors represent a significant proportion of cancers. Already in 1995,17,200 new cases of intracranial tumors were diagnosed **[1,2]**. Some data even suggest that 100,000 patients per year die from it with symptoms of intracranial metastases.

In developing countries, the fight against cancer (all types of cancer) remains a major public health challenge. As social security does not exist, the cost of the treatment is devolved solely to the patient. COTE D'IVOIRE does not disregard this rule even if considerable efforts are made, such as the recent free access to certain drugs used in first-line cancer treatment.

In this fight against cancer, early diagnosis allows a better follow-up rate and this requires new imaging techniques such as CT and MRI perfusion. The other challenge lies mainly in therapeutic evaluation because knowing whether a treatment will be effective for a patient according to certain parameters will allow a huge saving both in terms of time and money.

Even if its cost is still high in our African countries, CT is increasingly present in our hospitals and some of these parameters have proven to be very important in the diagnostic and therapeutic management of brain cancer **[2]**.

As a reminder, Angiogenesis is both a physiological and a pathological process (growth of new versels), without no cancer could exist. His study is one of the keys to the fight against cancer.

Thus, the study of angiogenesis has led to the development of a new treatment called targeted antiangiogenic therapy. These therapies target tumor vascularization by preventing its duplication. But the interest of its targeted therapies lies in the therapeutic follow-up of cerebral cancers. Indeed, an anti angiogenic treatment can be effective from the very first hours without this being detectable by known standard morphological imaging techniques. It therefore seems that predicting the response of bevacizumab treatment in brain tumors is a major challenge for oncologists and a challenge for radiologists because it will allow a better selection of treatment-ready patients, thus reducing the risk of therapeutic toxicity and everything that goes with it.

In our study we were interested in the functional imaging technique of PERFUSION. Whether performed by CT or MRI, infusion allows for better tumor characterization.

The objective of this study was twofold. First, to present the two FUNCTIONAL imaging techniques, perfusion CT and MRI perfusion, and their respective performance in characterizing brain tumors, and then to determine whether the quantitative parameters of perfusion CT could predict the effects of bevacizumab chemotherapy on patients with brain cancer based on the RECIST.1.1 **[3]** guidelines.

PART ONE: GENERALITIES

I-CEREBRAL TUMOR

I-1. Epidemiology (4.5.6)

Recent data show an increase in the overall incidence of central nervous system tumors, probably due to the aging of the population on the one hand, and to improved diagnostic tools such as the advent of new imaging techniques [4].

The epidemiology of cranioencephalic tumors is based on the collection of heterogeneous data (geographical origin, neurosurgical, radiological, anatomopathological data). The variability of its data makes it difficult to estimate their impact [4].

CBTRUS [5] is a specialized data collection registry in the United States, which has estimated the annual incidence of primary brain tumors at 18.28/100,000 inhabitants between 2002-2006, increasing to 20.59/100,000 inhabitants/year between 2005-2009[6].

In children, cranioencephalic tumors are the most frequent solid tumors (20% of solid tumors), with an annual incidence of 4.67/100,000 inhabitant in the US between 2002-2006[5] and increased to 5.13/100,000 inhabitants between 2005-2009[6].

Brain tumor mapping remains dominated by the supra-tensory region in adults and the posterior fossa in children. The incidence varies from one histological type to another. Astrocytic gliomas are the most common after brain metastases. Craniopharyngioma is the most common non-neuroepithelial tumor in children, it is observed in 1.2 to 2.6 100% cases with a peak frequency between 5-14 years in children and adults over 50 years of age

I-2 Classification of cerebral tumors.

Brain tumor classifications are diverse. They may depend on their histological aspect, their topography and the age of the patient.

I-2- 1- WHO 2017 classifications of tumors of the central nervous system [7].

As early as 1977, Bailey and Cuching's and Kernohan's studies laid the foundations for the classification of cerebral tumors.

This classification will be modified in 2000[8; 9], then in 2007[10] by the inclusion of new histological entities, recent molecular biology and cytogenetic data.

The WHO classification is universally recognized and constitutes a common language among neuroradiologists, neurologists, neurosurgeons, anatomopathologists and neuro-oncologists.

This is a neuropathological classification based on the morphological characteristics of the tumor tissue, namely:

- The nature of tumor cells,
- Cell differentiation and density,
- The presence of cytonuclear atypia,
- Mitotic activity,
- Necrosis,
- Endothelial proliferation.

This classification distinguishes three types of tumors: primary tumors which will depend on the histological elements from which they are derived, secondary or metastatic tumors and bone tumors of the skull. Brain tumors are usually classified as:

- Intra-axial tumors developed from brain tissue

- Extra-axial tumors developed in the subarachnoid spaces (mainly from meningeal envelopes) or in the bone walls of the cranial cavity. All of its tumors can be either sus-tensor tumors located above the cerebellar tent or sub-tensor tumors located in the posterior fossa.

Tumors must be separated from adults and children, which are much rarer. Adult tumors are essentially supra tensor, those of children are willingly under tensor.

Tableau : Classification OMS 2007 des tumeurs du SNC [10]

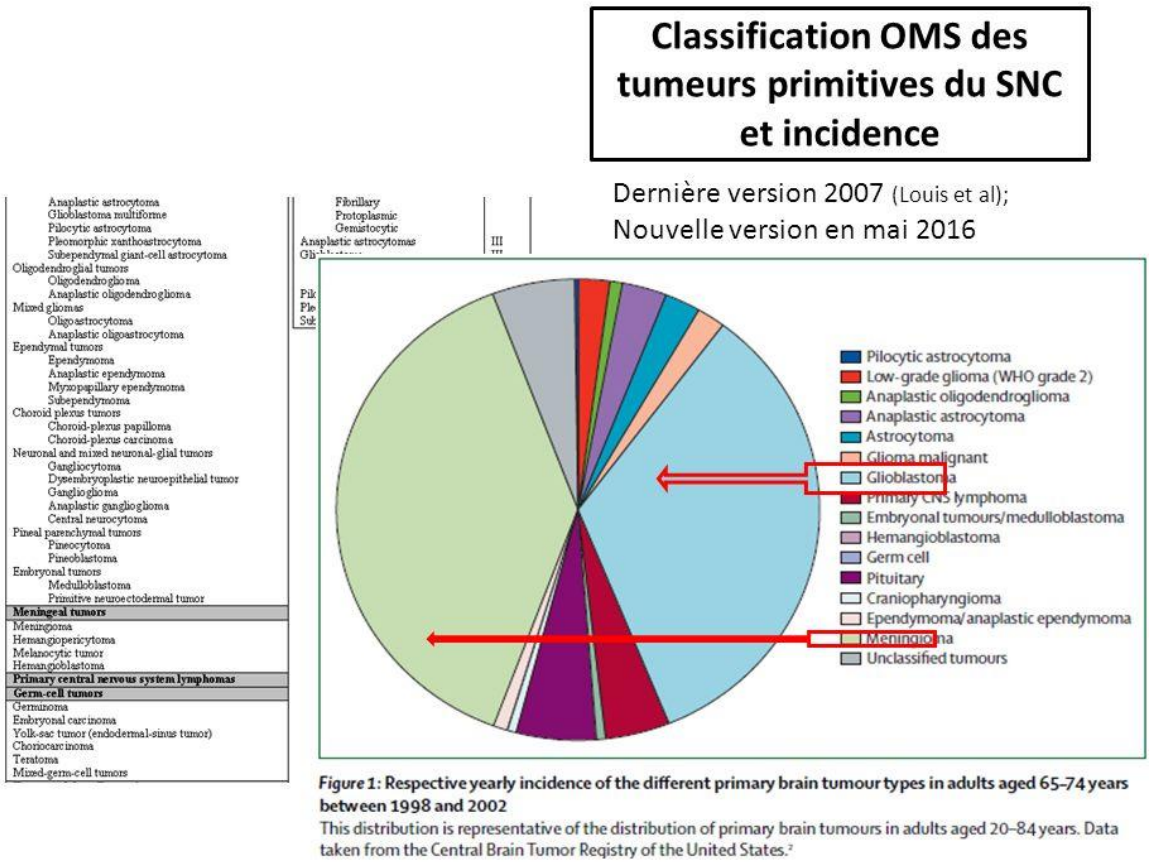


Figure 1: **Respective yearly incidence of the different primary brain tumour types in adults aged 65–74 years between 1998 and 2002**

This distribution is representative of the distribution of primary brain tumours in adults aged 20–84 years. Data taken from the Central Brain Tumor Registry of the United States.[2]

However, the advent of new imaging techniques has brought out the shortcomings of this classification. Indeed, it does not integrate clinical and imaging data [11]. This explains in particular a high rate of inter-observer discrepancy in terms of staging. Moreover, tumor heterogeneity would not be taken into account, resulting in impossible reproducibility.
In addition to the WHO classification recognized as a standard, there are other classifications, such as the Sainte-Anne classification.

I-2-2. Sainte-Anne classification of glioma

The lack of reproducibility of the WHO classification due to the use of subjective criteria (cell density, anaplasia, degree of differentiation) will be the subject of criticism by neuropathologist Catherine Daumas-Duport [8,12].For her, the exclusive consideration of the predominant cell type over the sample, while the relative proportion of cell types in a tumor varies from one sector to another in the same tumor, often leads to misinterpretation, with in particular the consideration of the reactive astrocyte component as the predominant tumor component.

These arguments led Daumas-Duport to present a classification of gliomas based on an integration of the clinic's data (in particular the patient's age, the chronology of symptoms, the presence or absence of neurological signs) and especially radiological data (mainly those of the IRM) in the histological study of tumors [13].

Two criteria, endothelial-capillary hyperplasia and contrast capture, make it possible to distinguish 2 grades of malignancy:

Grade A (low grade or benign): absence of endothelial hyperplasia and contrast recording.

Grade B (high grade or malignant): presence of endothelial hyperplasia and/or contrast recording.

The Saint-Anne classification distinguishes among the common forms of gliomas only three categories: oligodendrogliomas or oligo-astrocytoma of grade A or grade B and glioblastomas.

Glioma not taking the contrast: grade A oligodendrogliomas (or oligo- astrocytoma) (confirmed by the presence of isolated tumor cells with characteristic "button" nuclei).

Glioma taking the contrast: glioblastoma or oligodendroglioma (or oligo-astrocytoma) of grade B.

This classification has the disadvantage of applying only to astrocyte and oligodendroglial glial tumors and is not recognized by practitioners in Anglo-Saxon countries.

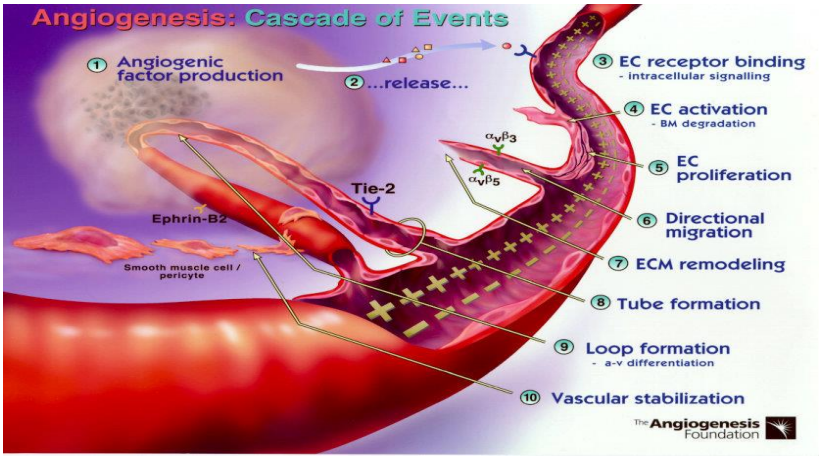
II-Angiogenesis tumor: state of the place

II-1. Physiological angiogenesis

II-1.1. Angiogenesis: Reminders [14].

Angiogenesis is the formation of capillaries from a pre-existing vascular network. Endothelial cells migrate, detach from the basement membrane and extracellular matrix. They multiply and organize themselves to form new vessels by budding from the parental vessel. The perished endothelial cells (pericytes, smooth muscle cells, fibroblasts) then develop, forming the final vessel. During adult life, the vascular network is stable and the angiogenesis process has been quiescent. However, physiologically, there are a few situations that cause this neovascularization process to be reactivated, such as physical exercise or during the maturation of the corpus luteum and uterine mucosa.

Illustration du processus d'angiogenèse



II-1.2 Role of VEGF [15]**.**

VEGF for "Vascular Endothelial Growth Factor" is the most important gene involved in angiogenesis. This gene allows the expression of 6 known glycoproteins that belong to the

family of angiogenic growth factors: VEGF-A (the most important, commonly called VEGF), VEGF B, C, D, E and placental growth factor PIGF.

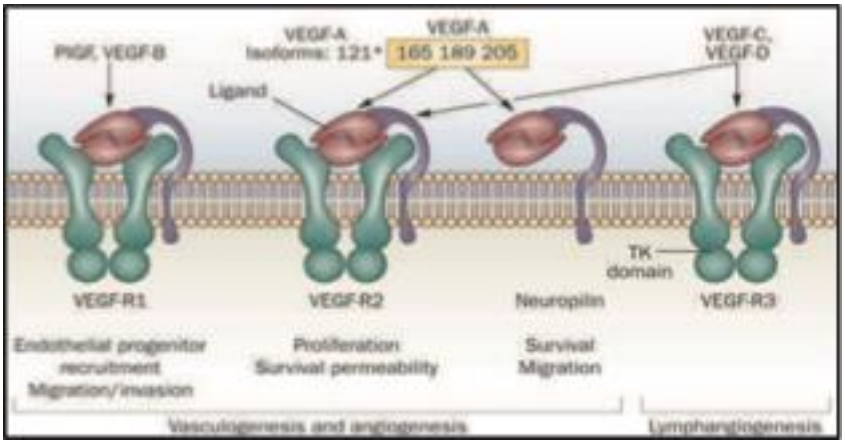
In vitro, VEGF is responsible for an increase in the survival, proliferation and invasion and migration capacity of endothelial cells. This induces the formation of capillary structures, there is also an increase in capillary permeability. In vivo, it is capable of causing the formation of new vessels [16].

There are four main isoforms of 121, 165, 189 and 205 amino acids of VEGF that interact mainly with two types of transmembrane receptors with tyrosine kinase activity called VEGFR-1 and VEGFR-2. VEGFR-1 and -2 receptors are present on the surface of endothelial cells as well as on the surface of hematopoietic precursors of endothelial cells. The activation of the transduction cascades is initiated by the connection of VEGF to its receiver.

VEGFR-2 is expressed in all endothelial cells, while the expression of VEGFR-1 in endothelial cells varies according to the type of vascular bed. A third receiver has been isolated, VEGFR-3, which binds in particular VEGF-C. This couple is involved in lymphangiogenesis.

Activated by VEGF, endothelial cells synthesize enzymes and proteins that degrade the extracellular matrix, thus facilitating the migration and invasion of endothelial cells to target tissues. VEGF is also a powerful factor in increasing vascular permeability.

The different types of VEGFR and their ligands (according to Grothey et al.) [17].



II-2. Tumor angiogenesis

II-2.1. Angiogenesis and cancer

For a tumor lesion to develop, it needs a supply of nutrients and oxygen, which is transported by the vascular network. The growth of a tumor therefore requires the development of appropriate vascularization.

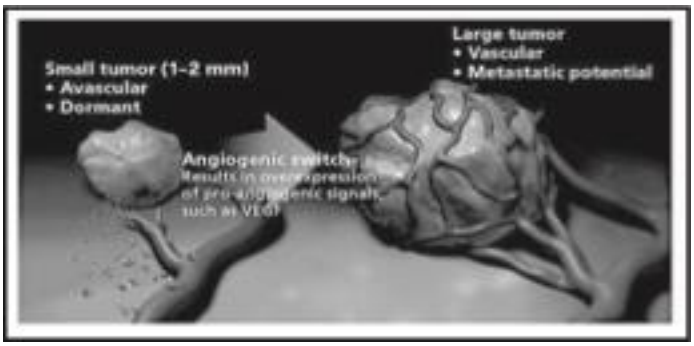
From 1971 FOLKMAN [18] hypothesized that the destruction of a tumor's feeding vessels could stop its evolution or even destroy the tumor. "The development of solid tumors is dependent on angiogenesis. Each increase in the tumor cell population must be preceded by an increase in neo-capillary.

II- 2.2. Concept of "Angiogenic Switch"

It must be understood that normal vessels and tumor vessels are opposed step by step. The former is considered as "dormant", while the latter are considered as "active". In the latency phase, there is a balance between pro- and antiangiogenic factors, tending to inhibit angiogenesis.

The "Switch" corresponds to the transition from the latency phase to the aggressive phase during which tumor neoangiogenesis begins. This occurs when the tumor measures about 1-2 mm3 [19]and is initiated mainly by hypoxia induced by cell proliferation in the center of the tumors. Endothelial cells are then activated by angiogenic growth factors, particularly VEGF, secreted by tumor and peri-tumoral cells, which also induce induction of membrane receptors to angiogenic factors. This is combined with an increase in vessel permeability under the action of VEGF due to the degradation of the extra-cellular matrix that destabilizes the interactions between pericytes and endothelial cells.

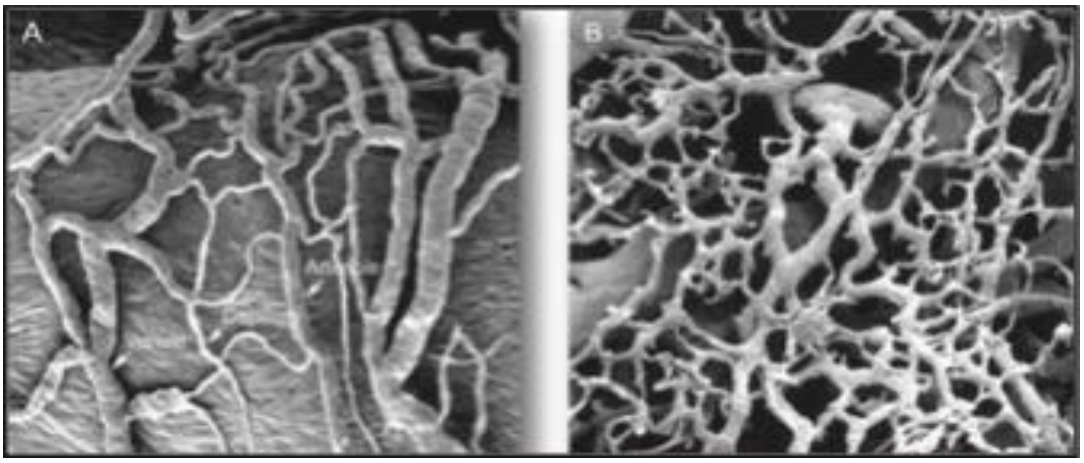
Illustration of the concept of angiogenic switch (Carmeliet et al.) [20].



II-2.3. Tumor vascularization architecture

The remodeling of tumor vessels is the consequence of these different stages of activation of the endothelial cell. The vessels are dilated, the pericytes detach and surround the capillaries. The result is a vascular budding that causes new vessels to form. The tumor vascular network is therefore opposed to the physiological vascular network both functionally and structurally. It is disorganized, unstable and uncontrolled in its location. Vascular lakes, hemorrhages and a passage of plasma fluid through the interstitial area are present within the body due to increased capillary permeability. Blood flow is heterogeneous and irregular, particularly due to the presence of arteriovenous shunts. This promotes hypoxia, which stimulates the production of angiogenic factors and maintains tumor growth.

Opposition between the healthy capillary network (A) and the tumor network (B), visualized under a scanning electron microscope



(A) (B)

II-3. Anti-angiogenic treatment: Bevacizumab

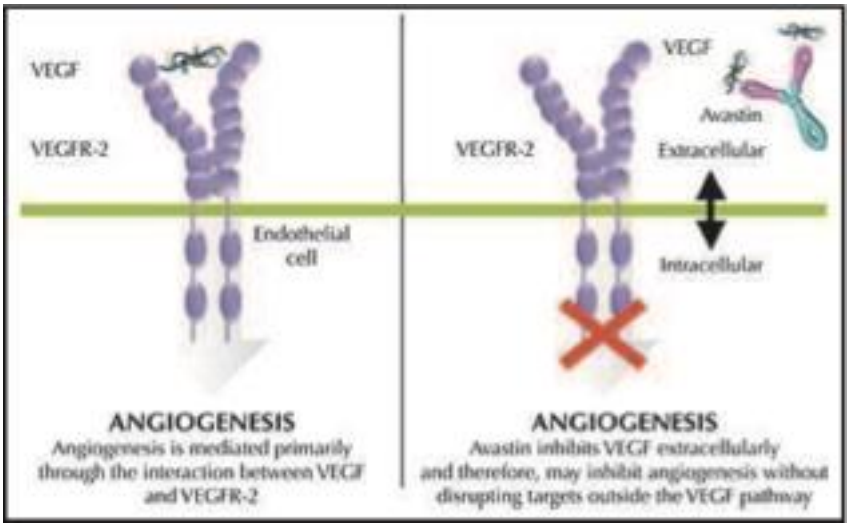
II-3.1 Molecule

VEGF and its receptors, through the reaction cascades they induce, are endothelial cell survival factors essential for tumor neoangiogenesis. New so-called "antiangiogenic" therapies, inhibiting this VEGF pathway, have been developed in recent years. The main molecules available on the market are the result of two different pharmacological approaches. On the one hand, molecules inhibiting the tyrosine kinase function of VEGF receptors such as sunitinb (Sutent®) and sorafenib (Nexavar®). On the other hand, molecules such as bevacizumab (Avastin®) which is an antibody against VEGF. Let's take a closer look at this last molecule

II- 3.2. Bevacizumab: General information

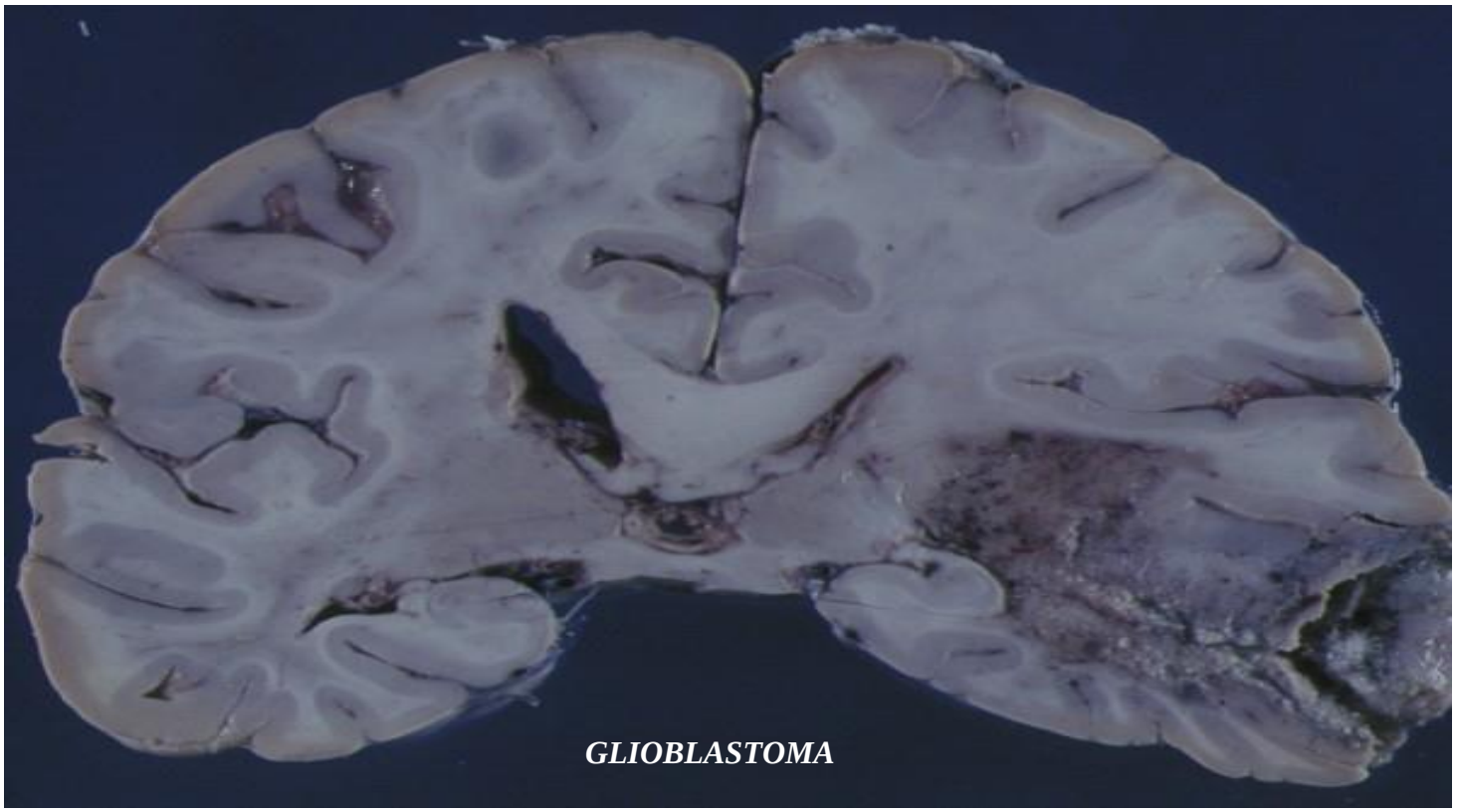
Bevacizumab is an anti-Humanized IgG1 monoclonal antibody to VEGF that binds selectively to human VEGF and neutralizes its biological activity. It has a strong affinity for an epitope present on all VEGF iso forms, partially overlapping the binding sites to VEGFR-1 and VEGFR-2 receptors, resulting in inhibition of VEGF binding to its receptors on the surface of endothelial cells. Inhibition of endothelial proliferation by bevacizumab blocks the neovascularization necessary for tumor growth and spread. This leads to cellular apoptosis and allows a decrease in intra-tumoral interstitial pressure, reducing the phenomenon of hypoxia and potentiating the action of the therapies used by allowing chemotherapy agents to reach tumor cells more easily. Bevacizumab therefore has an additive, or even synergistic, effect with "conventional" cytotoxic drugs. The blood half-life of bevacizumab is in the range of 17 to 21 days.

Mode of action of Bevacizumab

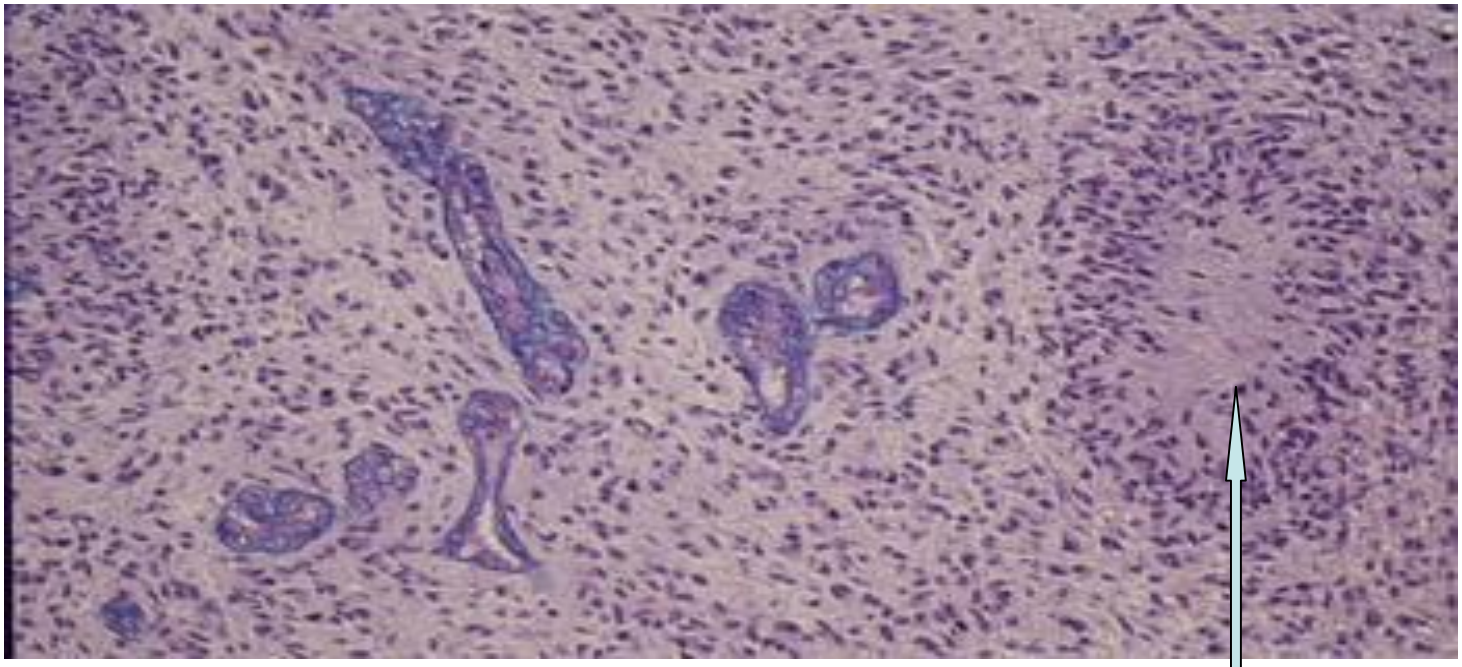


III- THERAPEUTICAL SCHEME IN THE CASE OF CEREBRAL TUMOURS [21].

The treatment of cerebral tumors was based on a combination of surgery and radiotherapy. Chemotherapy plays an increasing role. To better understand the involvement of BEVACIZUMAB we list here some clinical cases and the results of several published studies.



GLIOBLASTOMA



❖ Nitrosoureas

- Alkylants (adducts from l'ADN)
- BCNU (Belustine) per os

➢ Toxicity +++

- Hematological (platelets)
- Leukemogenes
- Pulmonary fibrosis (EFR ++++)
- Nausea (Let's get ++++)

- UNFC (Carmustine) IV
- Fotemustine (Muphoran)
- BCNU in a polymer matrix (Gliadel)

➢ Low response rate 10%. Uncertain impact on survival.

❖ Platinum (cisplatin or carboplatin)

❖ Irinotecan (anti-topoisomerase I)

❖ Etoposide (anti-topoisomerase II)

❖ Methotrexate (folic acid analogue)

* lymphomas

❖ Associations

PCV (procarbazine-carmustine-vincristine)
- Oligodendrogliomas (Cairncross, 1994)

Carboplatin-Etoposide
- Medulloblastoma and PNET

Oligodendrogliomas III (anaplastic)
Cairncross PCV schema (JCO, 1994)
- Belustine per os: 150 mg/m2 at D 1
- Vincristine: 2 mg IV to D7 and D 28
- Procarbazine (Natulan) per os 75 mg/m2/day from D 7 to D 28
- Resumption of the cycle every 2 months

Témodal: 200 mg/m2Day x 5 days / month

Oligodendrogliomas III (continued)

Search for co-deletion 1p/19q

- 70% of responses if deletion
- 30% if no deletion or only one deletion

First chemotherapy with PCV or Temodal

- Drugs after 2005.

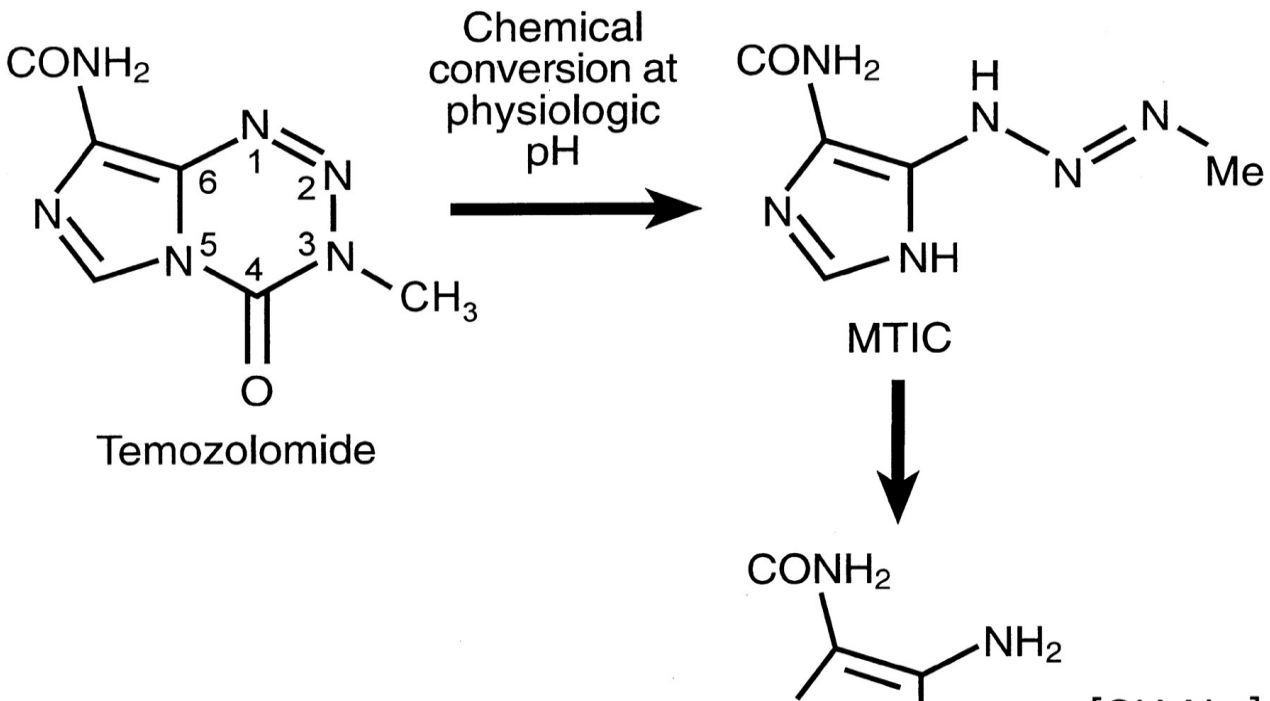
Temozolomide (Témodal)

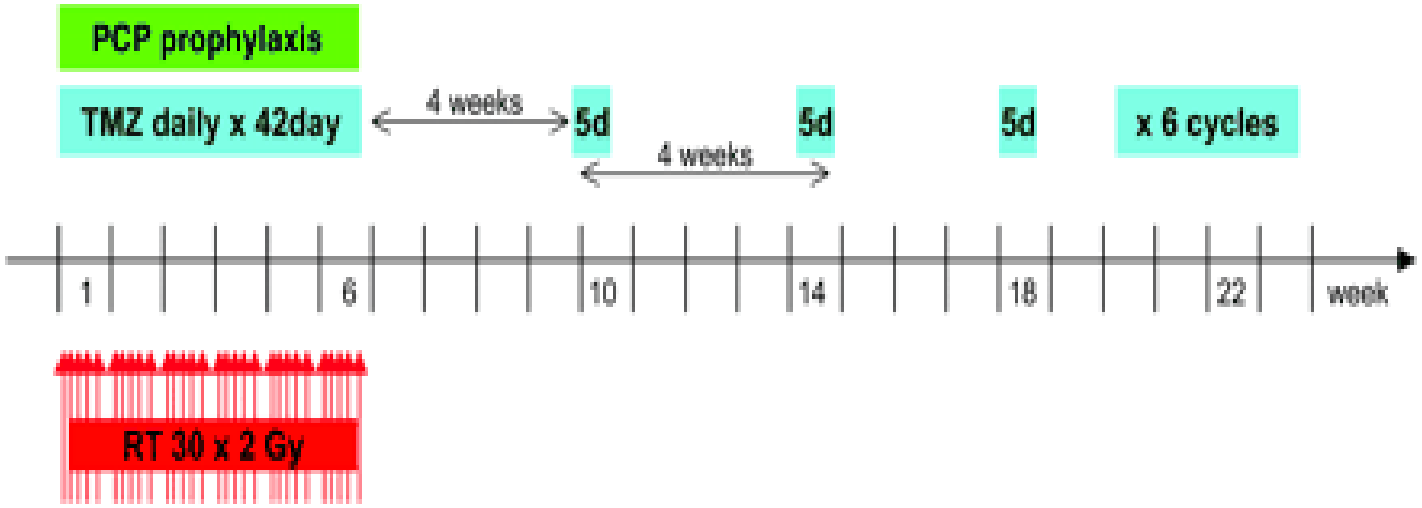
- Alkylant (adducts from l'ADN)
- Derivative of Deticène administered per os or IV

Toxicity

- Hematological (platelets, aplasia)
- Allergic rash
- Nausea (Let's get +/-)

Chemical structure of temozolomide.





RT: focal radiotherapy, 60 Gy in 6 weeks to tumor volume + 2-3 cm margin

TMZ: Temozolomide (Temodal®, Temodar®),
During RT: 75 mg/m² daily (including weekends) for up to 49 days.
Administration 1–2 hours before RT or in a.m. on days without RT.
Antiemetics: metoclopramide, only before initial doses needed.
Maintenance: 150–200 mg/m² daily x 5, for up to 6 cycles
Antiemetic prophylaxis with metoclopramide or 5HT3 antagonist

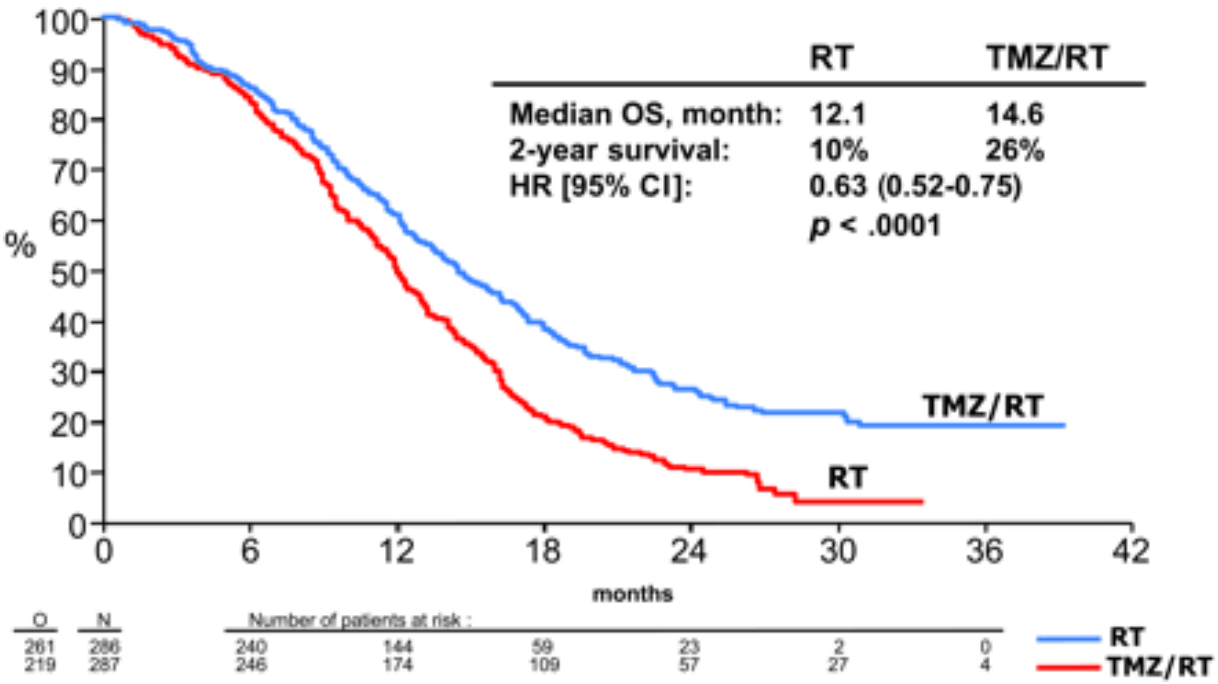
Pneumocystis carinii pneumonia prophylaxis during continuous TMZ administration only (lymphocytopenia) Pentamidine inhalations or trimethroprim/sufametoxazole 3x/week

the *O*3 position of adenine and the *O*6 position of guanine

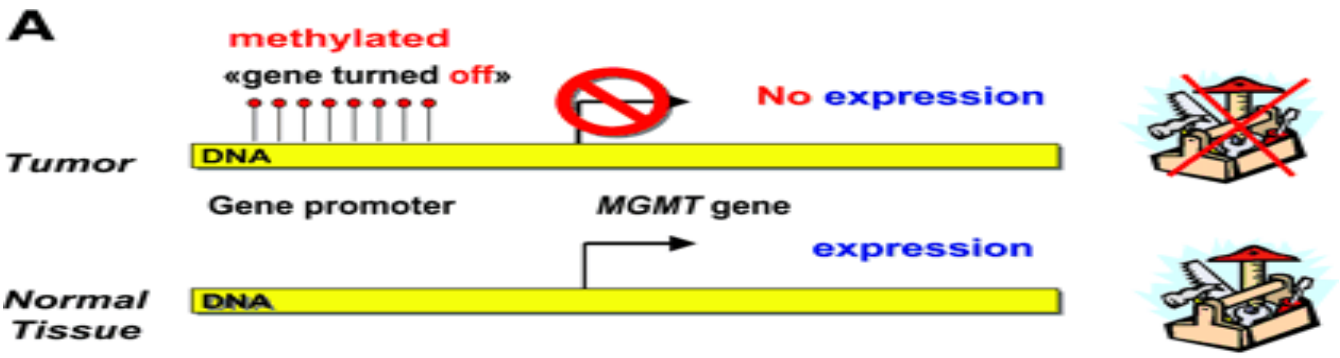
❖ Glioblastoma

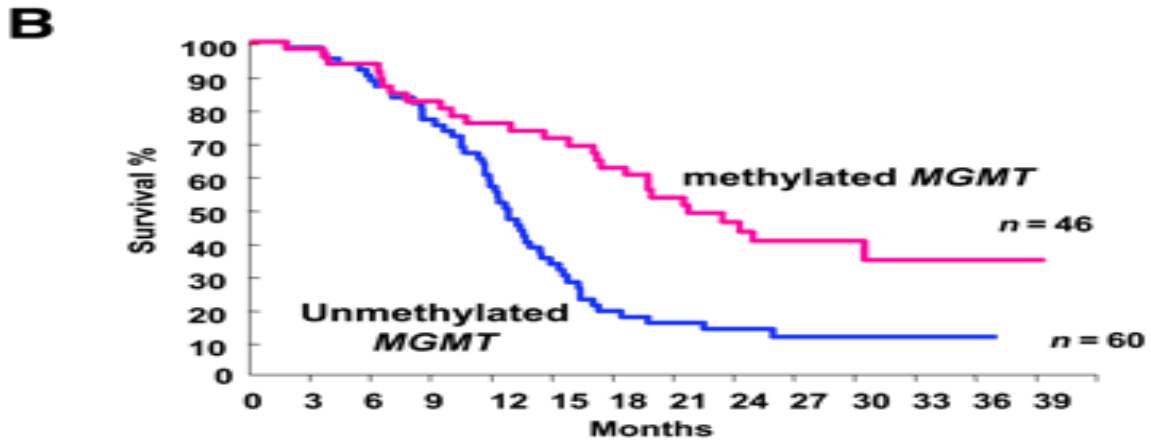
Stupp's diagram (NEJM, 2005)

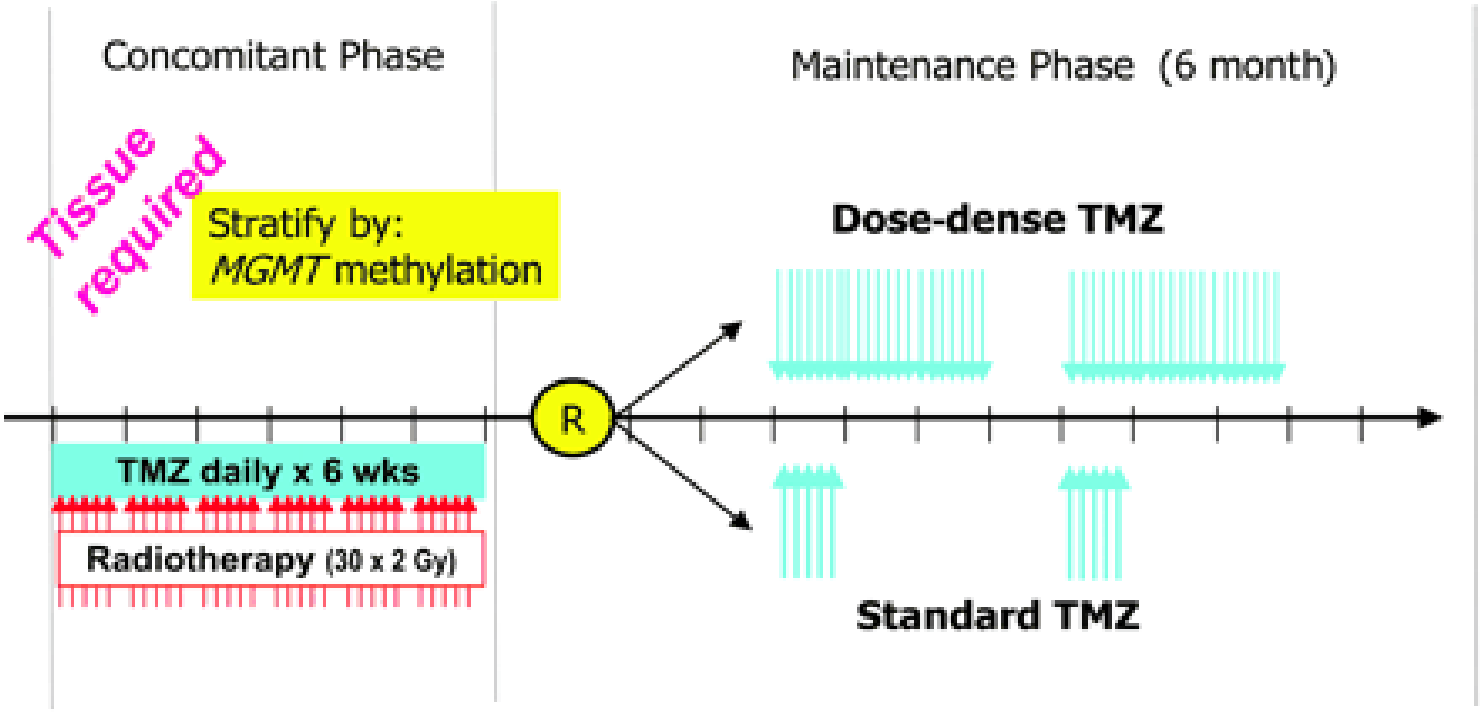
- Surgery if possible or stereotactic biopsy
- Then conformational radiotherapy (60 gy)
- Concurrent Témodal
- Témodal d'entretien x 6 months



From Stupp http://theoncologist.alphamedpress.org/cgi/content/full/11/2/165/F3


A
methylated
«gene turned off»
No expression
Tumor
DNA
Gene promoter
MGMT gene
expression
Normal Tissue
DNA


B
Survival %
100
90
80
70
60
50
40
30
20
10
0
methylated MGMT
n = 46
Unmethylated MGMT
n = 60
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Months


Concomitant Phase
Maintenance Phase (6 month)
Tissue required
Stratify by:
MGMT methylation
Dose-dense TMZ
R
TMZ daily x 6 wks
Radiotherapy (30 x 2 Gy)
Standard TMZ

EORTC TEST:Negatif

- Glioblastoma (recurrences)

✓ Semi-continuous Témodal

- 75 mg/m2/day x 21 days/28

✓ Belustine

- per os: 150-200 mg/m2, every 2 months
- IV: 60 mg/m2/day x 3 days every 2 months
- 10% of responses => ? ????? Survival?

✓ New drugs

- bevacizumab (Avastin)

- Glioblastoma (recurrences, continued)

Vredenburgh: IRINOTECAN + AVASTIN

(ASCO 2006)

✓ Irinotecan

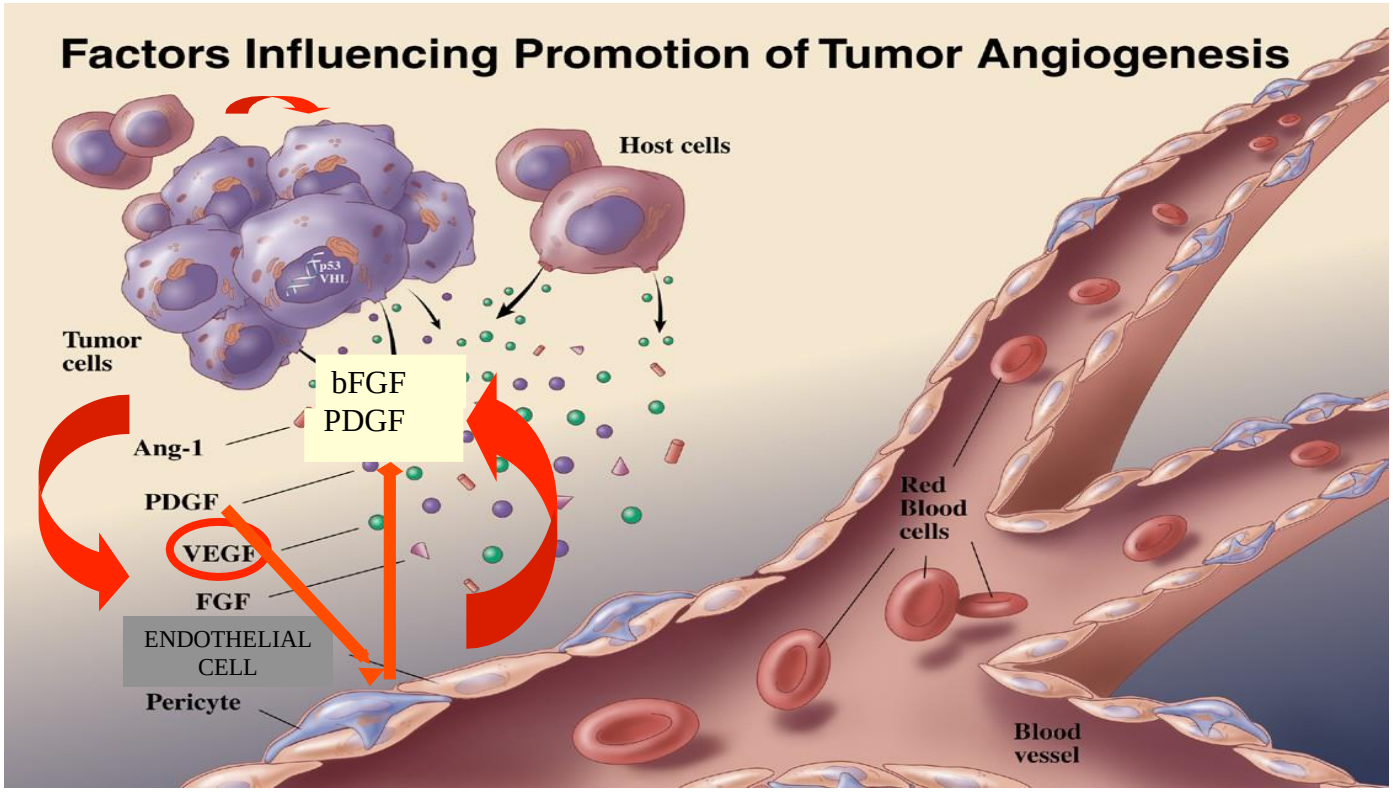
- 200 mg/m2 (if non-inductive anticompetitive)
- 400 mg/m2 (if inductive anticomitials)

✓ Bevacizumab (Avastin), anti-VEGF monoclonal

- 10 mg/kg

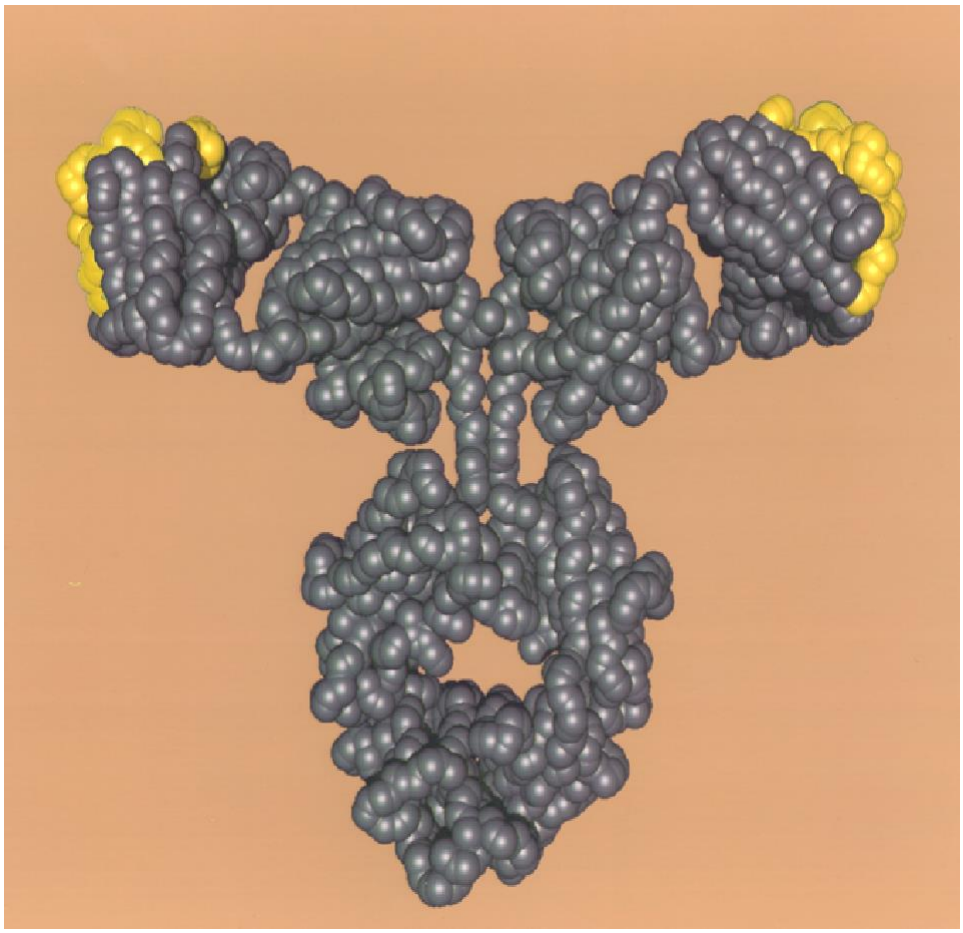
✓ One cure every two weeks

❖ Modulators of vegf

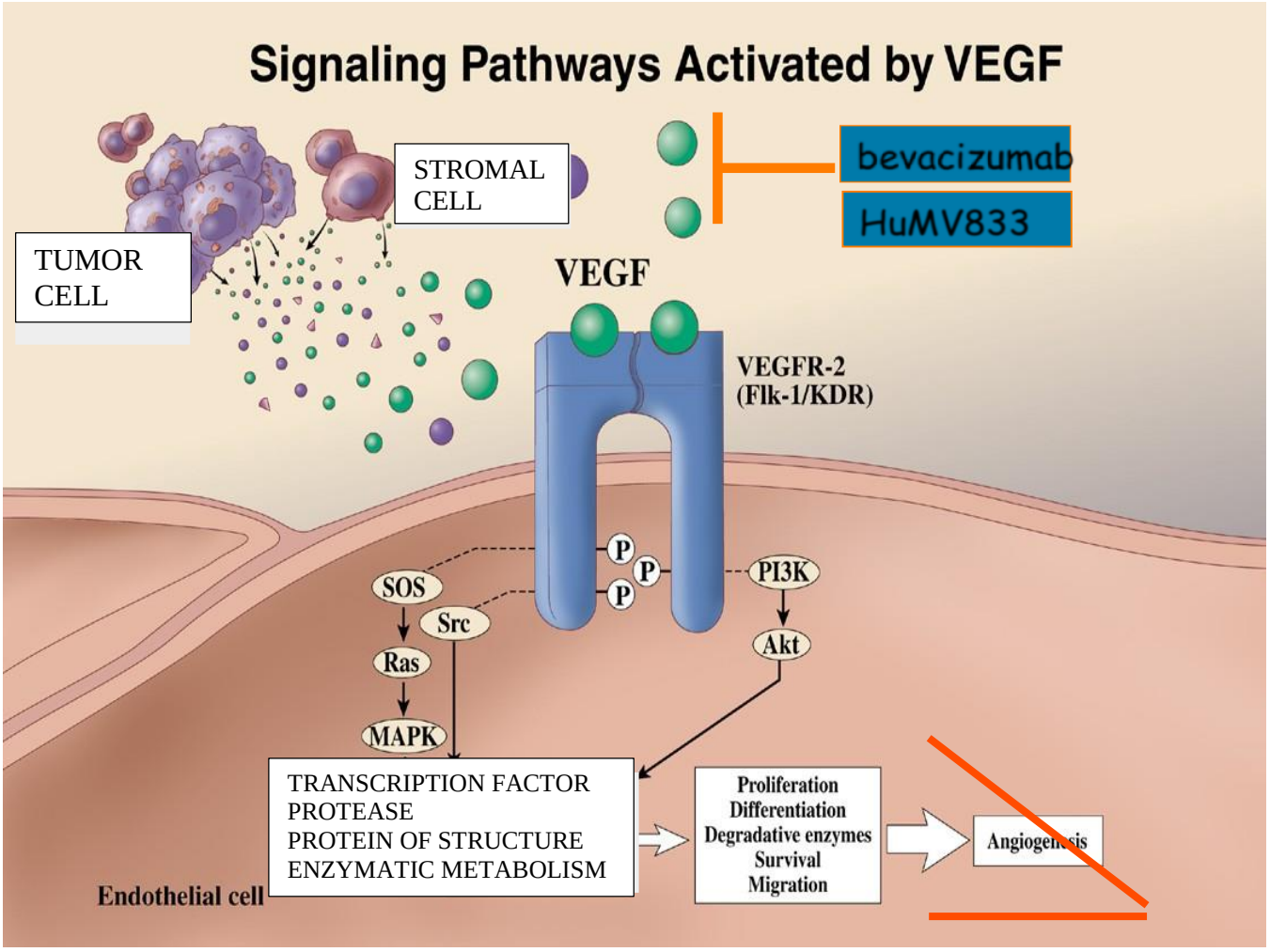


❖ **AVASTIN™**

(RECOMBINANT HUMANIZED ANTI VEGF AC)



- 93% human, 7% murine
- Recognizes all VEGF isoforms
- Kd = 8 x 10-10 M
- - Half life 17-21 days



❖

Bevacizumab / irinotecan
(avastin / campto)
In recurrences of high-grade glioma (results on 10 patients)

*Séverine Guiu *, Nicolas Isambert *, Michel Flesch, Pierre Fumoleau*, Annick Desjardins* *, Bruno Chauffert **

* Centre GF Leclerc, Dijon

*** Brain Tumor Center , Duke University,Durham NC**

- Experience of the brain tumor center, duke university (durham, n)

Asco may 2006 *

* published in clinical cancer research (j. Vredenburgh, feb 2007)

Phase 2 study, prospective, 32 patients

- high-grade glial tumours: 9 gr iii, 23 gr iv

- recurrence after radiotherapy ± chemotherapy

- bevacizumab / irinotecan every 15 days

Results :

- 20/32 (63%) imaging responses: 19 rp, 1 rc gr iii : 6 rp, 3 stable

Gr iv : 1 rc, 13 rp, 8 stable, 1 progression

- survival without progression at 6 months: 38% (median: 23 weeks) gr iii : 56% (median = 30 weeks)

Gr iv : 30% (median = 20 weeks)

- overall survival at 6 months: 72%.

BEVACIZUMAB	IRINOTECAN
- Glial tumors * hyper-vascular * secrete VEGF - Avastin * Anti-angiogenic * Humanized monoclonal acid * traps the circulating VEGF - Indicated in colorectal cancer, breast, lung and kidney	- Campto - camptothecin derivative - topoisomerase inhibitor i - good penetration of the blood-brain barrier - active as monotherapy in recurrent glioma: - response rate from 0 to 15%; - 6-month ssp 20% 20% ssp (friedman, duke university, jco,1999)

Avastin / campto: 1st line ma in metastatic colorectal cancer

- Description of the 10 patients

- inclusion: may 2006 to february 2007

- recurrent gliomas:

7 glioblastomas, 1 grade iii astrocytoma, 2 b oligos

7 men / 3 women. Median age: 43 years[28-57]

- Initial Treatment:

Surgery: 4/10

rt: 2 / 10

rt + témodal: 3 /10

chemotherapy alone: 1 /10 (pcv)

Duke university treatment administration scheme

- Irinotecan:

- 125 mg/m2 iv infusion of 90 min if absent anti-competitive agents (9/10)

- 340 mg/m2 iv infusion of 90 min if anti-competitive agents (phenytoin, carbamazepine, oxcarbazepine, primidone, phenobarbital) (1/10)

➢ Bevacizumab:

- 10mg/kg as a 90min iv infusion

➢ 1 cycle every 15 days

- Follow-up

➢ Evaluation every 2 months (mri)

▪ Mac donald's criteria:

- product of 2 orthogonal mri diameters

-dose of corticoids

-clinical response

➢ Surveillance

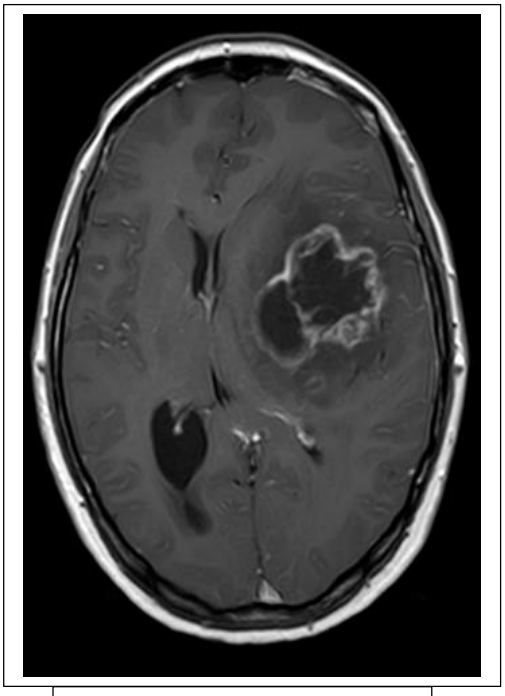
▪ Nf-blood platelets

-pnn>1500/mm3; inserts>100 000/mm3

▪ Ionogram, creatinine, liver enzymes,

▪ Blood pressure + urine test strip

- Results:

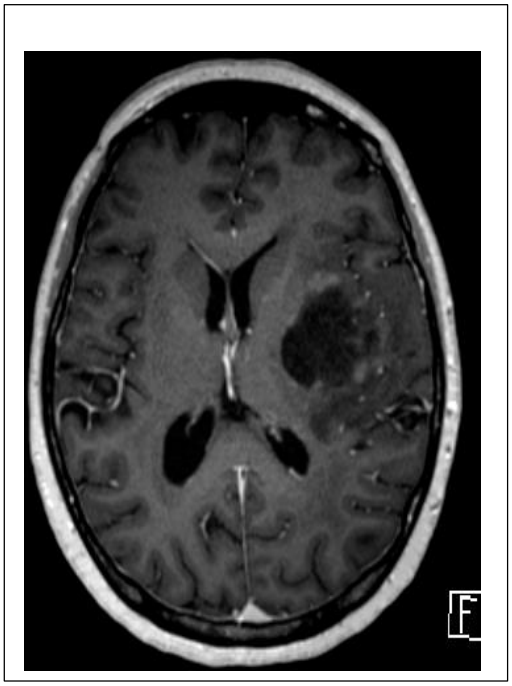


INITIAL MRI

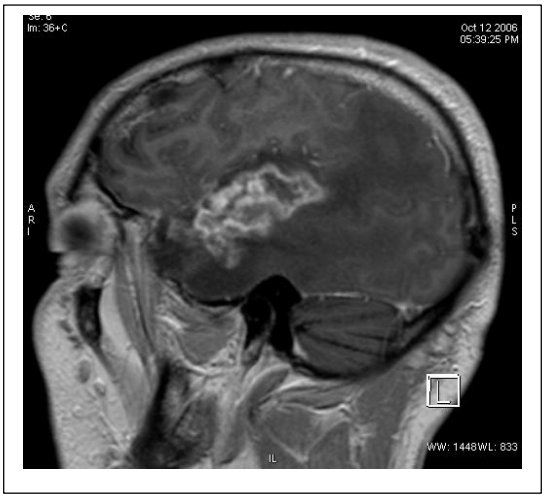
- 40-year-old patient
-oligodendroglioma b
- initial rt (08/2005)
- recurrence: pcv then témodal failure
- hemiplegia+ aphasia
- solupred 120mg/day

regression of
Hemipleia and aphasia
↓solupred 80mg/day
Imr response : ↓32%

Treatment still in progress
ssr:6 month +

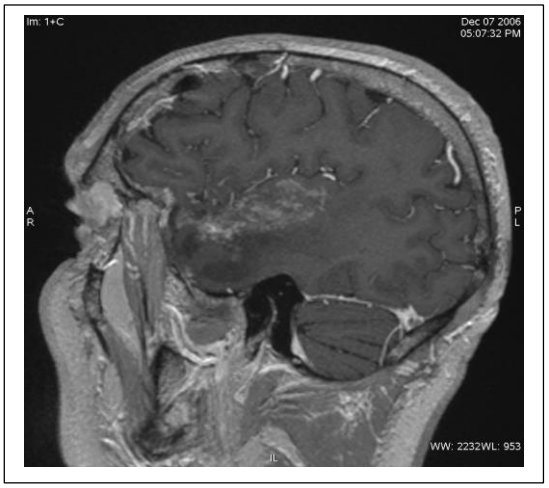


RESPONSE AFTER 2 MONTH

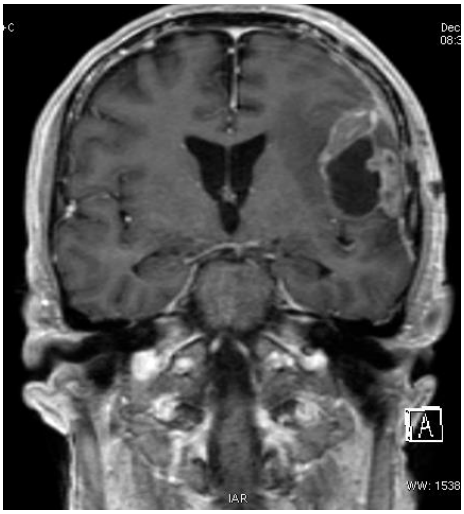


INITIAL MRI

- 42-year-old patient
-Glioblastoma
-Surgery+ stupp(08/2005)
-reccurence treated with semi continuous temodal ⇒failure
-Behavioural disorder
-no corticosteroids



RESPONSE AFTER 2 MONTH



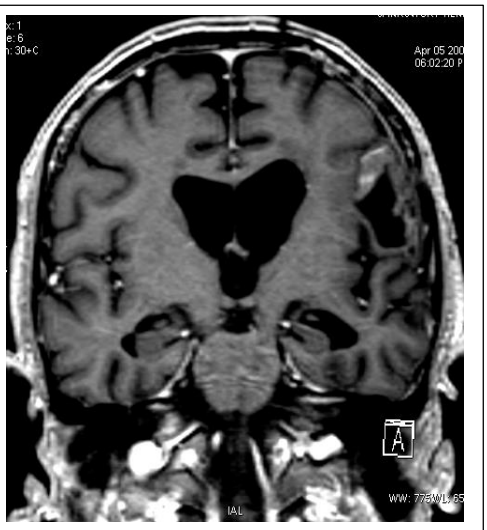
- 56-year-old patient
- astrocytoma gr iii
- initial surgery + stupp (07/2006)
- progress under temodal
- partial hemiplegia+dysphasia
- solupred 140mg/day

Clinical improvement

solupred idem

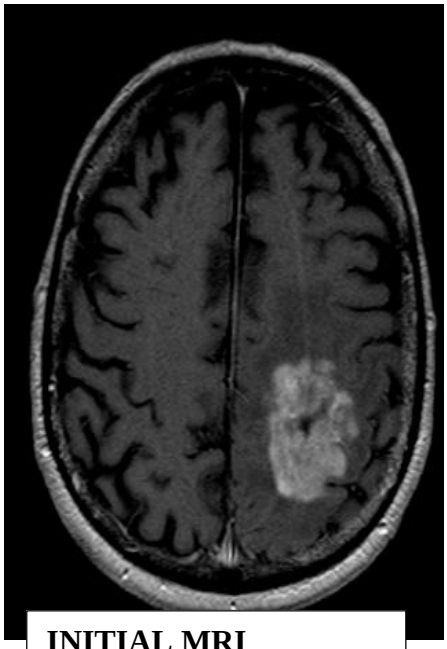
Mri response :↓51%

Treatment still in progress
Sss :4 month+



INITIAL MRI

RESPONSE AFTER 2 MONTH



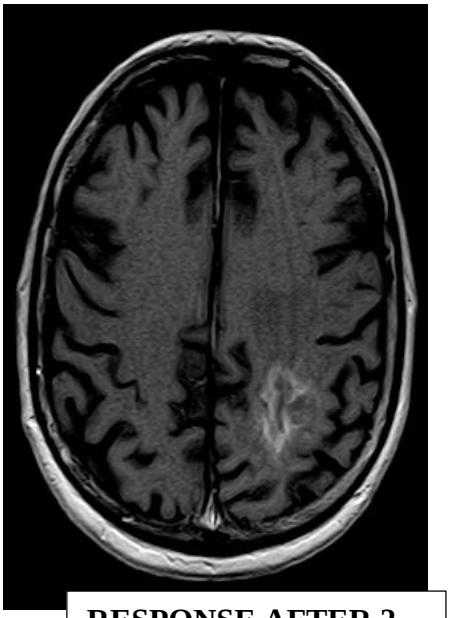
INITIAL MRI

51-year-old patient

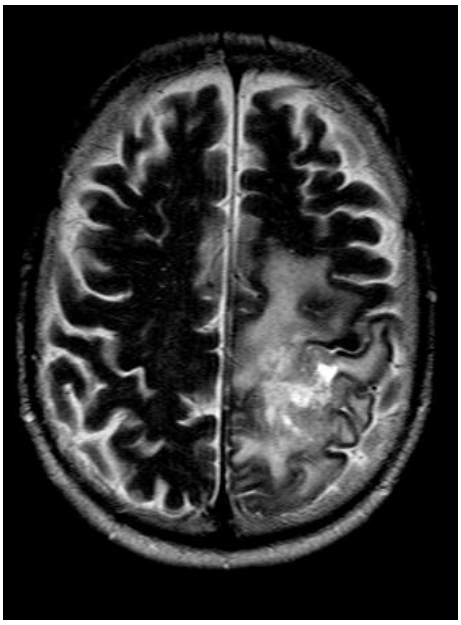
-oligodendroglioma a
- rt only (06/2003)

- recurrence treated by témodal (04/2006)

- hemiparesis, sensory disorders, fp
- solupred 40mg/day



RESPONSE AFTER 2 MONTH

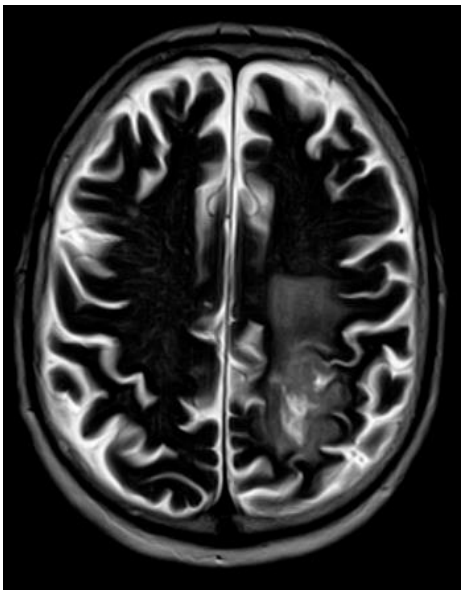


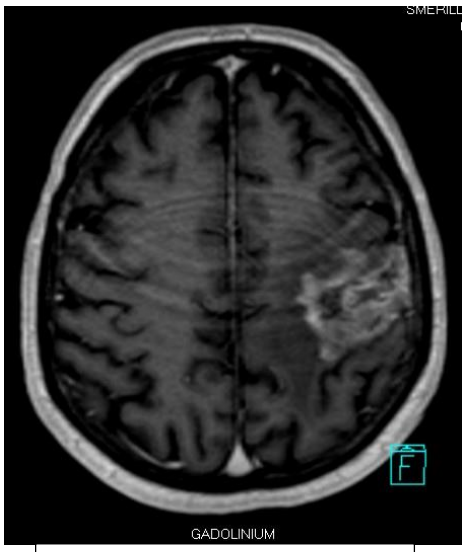
Clinical improvement

Solupred idem

MRI RESPONSE:↓62%

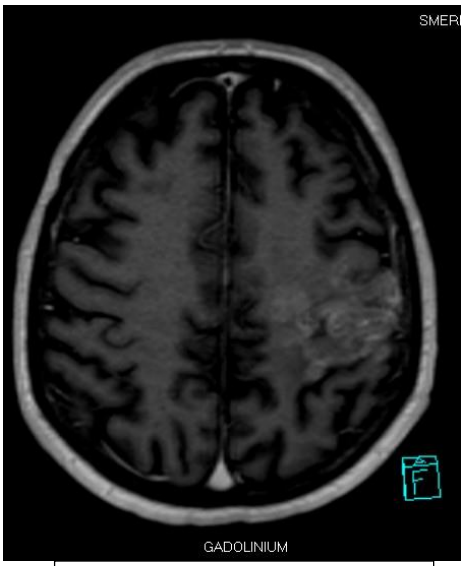
Treatment still in progress
SSS :4 month+



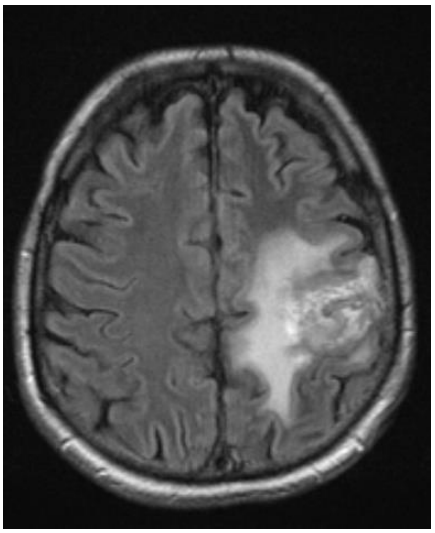


INITIAL MRI

51-year-old patient
- glioblastoma
- initial stupp (01/2006)
- progress under témodal then bicnu
- hemiplegia + aphasia
- solupred 60mg/day



RESPONSE AFTER 2 MONTH

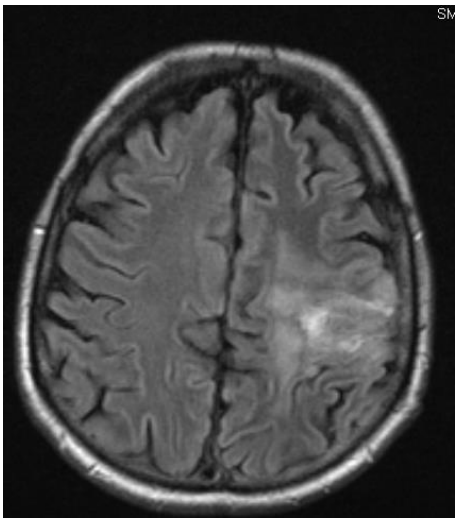


Clinical stabilization then evolutionary recovery

Solupred:40 mg/j

Response:↓12%

CURRENTLY PALLIATIVE CARE (SSR 6month)



- 52-year-old patient, glioblastoma, progression under Stupp:

>MRI response = 19% and clinical improvement during 4 cures

>Currently palliative care: SSR 10 months

- 47-year-old Patient, glioblastoma, initial surgery and ongoing progression of Stupp:

>MRI response = 35%.

>Treatment still in progress (SSR 3 months +)

- 3 patients (2 GBM, 1 oligo B): death

- Results

- Clinical responses

- Improvements: 6
- Stabilization: 1
- Death: 3

-Imaging responses

- ↓10-30 %: 2
- ↓30-50 %: 3
- ↓50-70 %: 2
- Unevaluable

According to Mac Donald's criteria

- RC: 0
- RP: 2
- Minor responses and stabilizations: 5
- Progress: 0

- Toxicities

- No hematological toxicity ++
- 5 diarrhea, 1 nausea & vomiting
- 2 epistaxis
- 1 digestive ileus
- 1 PVT
- 1 episode of urinary infection
- 1 suspicion of leukoencephalopathy at Avastin® (regressive coma if stop

- Conclusion

Short series in accordance with the results of Friedman et al from Duke University

- No complete response but possibility of partial responses or lasting stabilizations

- Constant decrease in contrast taking even if tumor dimensions vary less

- 3 early and rapid deaths (1 suspected leukoencephalopathy at Avastin)

- 2 deaths have occurred on massive diseases

- Prospects for the future

Legitimate prescription in practice by recalling in the PPS the reference: Vredenburgh JJ, Desjardins A, Herndon JE 2nd, ... Friedman HS. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res. 2007 Feb 15;13(4): 1253-9.

- Early integration of the neo-adjuvant scheme for GBMs not resectable before Stupp? ANOCEF Project? PHRC?

- Perfusion MRI to be assessed

  -Limitations of Mac Donald's criteria

IV- FOLLOW-UP OF THERAPIES ON IMAGING

IV- 1. Therapeutic follow-up: recist criteria

Therapeutic evaluation is one of the main roles of cancer imaging. This

Changes in the number and size of measurable tumor "targets" allow us to make this assessment.

Then imaging helps us to make therapeutic decisions in the management of patients treated "routinely" with drugs of known efficacy. The purpose of imaging here is to guide the oncologist in his treatment choices.

In these both situations, the evaluation of therapeutic response is obtained by estimating the tumor volume. The validation of morphological criteria therefore required the creation of standardized, reproducible tools in order to standardize evaluation criteria, particularly in the context of clinical trials.

In 1979, the World Health Organization (WHO) defined criteria based on the two-dimensional measurement of lesions in CT scans or standard radiography [22].

In 2000, an expert group of European, American and Canadian cancer research organizations (EORTC, NCI, NCIC) [23] established new criteria for evaluating response to treatments in clinical trials to address inaccuracies in WHO criteria. Now known as RECIST (Response Evaluation Criteria in Solid Tumors) criteria, they apply only to solid tumors, based on the one-dimensional measurement of lesions with the objective of simplifying and standardizing the evaluation criteria for clinical trials. In 2009, these criteria were updated to version 1.1. [24].

The RECIST group sets very precisely the tumor targets that can be taken into account, gives recommendations on the imaging methods to be used and establishes rules for evaluating the response.

The scanner remains the most suitable examination until now because it is a fast, reproducible method that allows a "whole body" examination. It is this modality that is routinely used in the monitoring of patients with a history of cerebral tumor.

For each patient, the largest diameter of 1 to 2 lesions greater than 10 mm per affected organ is measured, without exceeding 5 lesions in total. These "target lesions" chosen by the operator will serve as a "common thread" for judging the tumor response in a given patient. The sum of these diameters defines the tumor "volume" that will be used to calculate the evolution.

Some lesions called "non-target lesions" are only involved in the development of the tumor response if they progress or disappear. They correspond either to measurable lesions that are not defined as a target by the radiologist or to lesions that cannot be evaluated.

The "Baseline" is the so-called reference examination, it is essential because it is from this last one that the choice of the different target lesions will be made. As long as the patient is receiving the same treatment, the response will be assessed on the basis of this examination. "Nadir" is the best response to treatment and is the test to which any new test must be compared to judge tumor progression.

Surveillance evaluates: measurable lesions, the evolution of non-measurable lesions and the appearance of new lesions. The response criteria are: progression if the increase in tumor size is greater than 20% or appearance of a new lesion and regression if the tumor size decreases by 30% or more. For intermediate cases, we speak of stability.

Schematic illustration of RECIST 1.1 [24] response criteria

IV- 2. Limitations of the RECIST criteria

The appearance of targeted therapies such as bevacizumab challenged these criteria because of the few effects on the tumor size of these treatments, while the effect on survival was very quickly positive in patients assessed as "non-responders" according to the RECIST criteria.

For bevacizumab, VEGF inhibition induces a reduction in the number of micro vessels found on treated experimental tumors [25].Histological analysis shows that anti-VEGFs are responsible for this standardization of the architecture of micro vessels. These microscopic transformations are accompanied by functional modifications with, on the one hand, a reduction in capillary flows that become unidirectional again and, on the other hand, a decrease in permeability. These changes in microcirculation have a cytostatic action that blocks tumor progression and promotes the development of necrosis [26]. The effect on the reduction in the dimensions of tumor lesions is only very moderate, but the RECIST evaluation, based solely on dimensional criteria, cannot be fully transposable in these patients receiving antiangiogenic treatment. It does not take into account the tumor devascularization induced by these treatments, which is a good sign of response to treatment without any change in size [27].

IV- 3. Development of new imaging monitoring tools

In order to evaluate the response to these new treatments, an approach is represented by functional imaging. Also called angiogenesis imaging or microcirculation imaging, this modality does not seek to visualize microvessels but allows to detect disturbances in their mode of operation.

Indeed, as explained above, tumor angiogenesis is particular and differs from that of normal capillaries. It consists of immature, tortuous and irregular vessels responsible for ineffective infusion. Vessels have increased capillary permeability causing extravascular leakage, especially to macromolecules, and do not respond to the usual mechanisms for regulating blood flow.

Microcirculation imaging allows functional abnormalities to be measured based on the progression of tracers in the microvessels and through the capillary wall. This is why it tends to become one of the main themes of imaging in addition to traditional morphological tumor evaluation. The in vivo study of tissue perfusion by perfusion imaging includes many clinical applications such as lesion diagnosis, tumor characterization, assessment of tumor aggressiveness, determination of prognostic factors, detection of occult metastases, and prediction and monitoring of treatment response [28].

Let's take a closer look at this microcirculation imaging, which seems to provide very important answers in the study of cerebral tumors

V-IMAGING OF MICROCIRCULATION

V-1. Perfusion parameters: definition

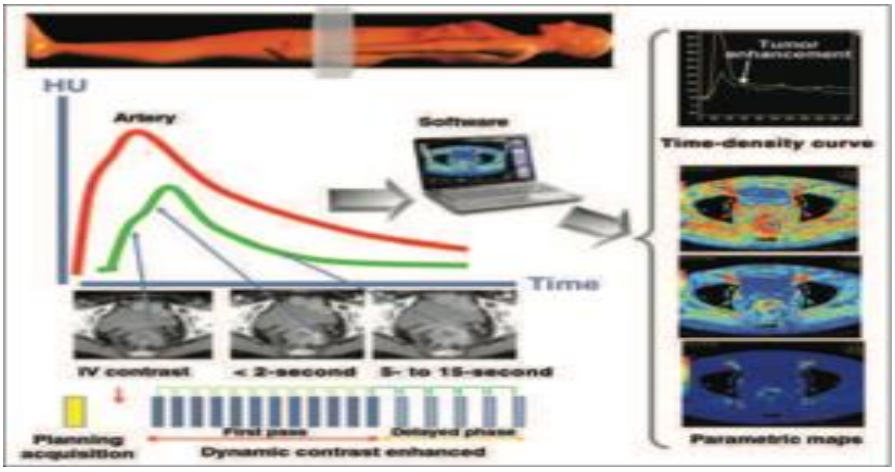
Perfusion imaging allows the microcirculatory network to be characterized using physiological parameters:

Tissue perfusion, also called blood flow (F or BF: blood flow), is the blood flow in the lumen of micro vessels in a volume of tissue. It is expressed in milliliters per minute per 100 g of tissue (mL/min × 100 g).

The tissue blood volume or blood volume fraction (BV: blood volume) corresponds to the volume of blood present in the capillaries contained in a volume of tissue. It is expressed in milliliters per 100 g of tissue (mL/100g).

Mean transit time (MTT) is the average residence time of the contrast material at a given tissue site, which is equivalent to the average time it takes for blood to cross the capillary network (time between arterial entry and venous exit). It is expressed in seconds (sec.).

The surface permeability (PS) product corresponds to the flow of molecules through the capillary membranes into a certain volume of tissue. It is the product of permeability by the total surface area of capillaries within a mass of tissue. It quantifies the diffusion of contrast media in the interstitial space, reflecting capillary permeability. It is expressed in milliliters per 100 g of tissue (mL/100g).



V-2. **Perfusion CT (PCT) (29)**

V-2.1 Principle

The principle of perfusion CT is based on the analysis of the evolution of the contrast medium during the first passage of an intravascular bolus of an exogenous non-diffusible agent: iodine. Information on cerebral hemodynamic parameters is thus available, which is made easy to read by color functional maps.

The acquisition is made by a dynamic mode scanner during the intravenous peripheral injection of an iodized contrast agent. Based on the images obtained during dynamic acquisition, image analysis software provides quantitative functional information on brain perfusion parameters. It automatically calculates the characteristic parameters of brain perfusion according to a mathematical model.

The theoretical aspects of perfusion CT were developed more than twenty years ago, and validated in animals and in clinical trials, against infusion CT-Xenon and MRI

The four characteristic parameters of brain perfusion calculated are represented on a curve:

- TTM (Mean Transit Time, MTT), in seconds, represents the average time interval required for a bolus of iodized contrast material to pass through the cerebral capillary network;
- CBV (Cerebral Blood Volume, CBV) in ml/100 g of tissue, refers to the fraction of parenchyma occupied by the blood vessels;
- CBF (Cerebral Blood Flow, CBF) in ml/100 g tissue/min;
- the time to the maximum contrast enhancement peak or Time To Peak (TTP), in seconds.

There are three mathematical models for calculating time-intensity data:

- the maximum slope model used by Siemens. Based on the Fick principle, the CBF is calculated according to the maximum slope of the curve of each voxel divided by the maximum arterial elevation (actually

evaluated by the placement of an area of venous interest on the upper sagittal sinus, thus correcting the partial volume effect). This model underestimates regional brain blood flow values and does not highlight the contrast between grey and white matter perfusion, even with adequate post-processing of the data;

- the balancing indicator model which mainly applies to diffusible indicators, used in nuclear medicine and with Xenon CT;
- the central volume principle, developed by Philips Medical Systems, the model used by our team. It is based on the calculation of the TTM which results from a mathematical operation of deconvolution of the parenchymal enhancement curves by a reference arterial curve, generally selected at the level of the anterior cerebral artery.

The second parameter evaluated is the CBV, whose calculation is based on the partial volume effect. It is represented by the area under the curve of a pixel at the parenchyma level divided by that of a reference pixel with no partial volume effect (venous output function taken at the level of the upper sagittal sinus). Its final calculation is made taking into account also the hematocrit.

The cerebral blood flow is finally calculated according to the DSC = VSC/TTM formula.

For infusion CT protocols involving low injection rates ($\ll$ 5 ml/sec) of contrast media, the best model for analyzing infusion CT data would be the one based on the central volume principle

V.2.2 Perfusion CT technique

The acquisition is carried out on a multi-bar spiral scanner (16 bars preferably)
A CT scan before injection is first performed, allowing a preliminary identification necessary for the choice of the reference level, depending on the pathology explored, centred on the region of the central grey nuclei in vascular pathology, or centred on the tumor.
The next step is the acquisition of images in dynamic mode, at the rate of four 5 mm thick joint sections each for 40 seconds (one image every two seconds), during the intravenous peripheral injection of a 40 ml bolus of iobitridol 300 mgI/ml, G at an injection rate of 4 ml/sec into a peripheral vein, using an automatic injector. The acquisition parameters are a voltage of 90 kV and an amperage of 120 mA, 90 kV giving a better compromise between quality and exposure than 120 kv. The injection time is 10 seconds. The acquisition starts simultaneously with the injection and lasts 40 seconds. During this period, 80 images are acquired, i.e. 20 images for each of the 4 cutting levels, with a rate of one image every 2 seconds. This protocol therefore makes it possible to obtain four 5 mm thick cerebral CT cuts, i.e. a volume of 20 mm. When reconstructing the data, two 10 mm volumes can be obtained, which improves the signal-to-noise ratio.

V-2.3. Advantages and limitations

Perfusion CT is easily accessible, especially in emergency, and can be integrated into the patient's initial lesion assessment with conventional CT; it provides absolute brain perfusion

data. These properties are major advantages over other perfusion imaging techniques. Under good acquisition and analysis conditions, infusion CT gives accurate and reliable results. The spatial resolution is excellent (1-2 mm). The results of the infusion CT scan are available within minutes.

The anatomical field explored remains weak for the moment (a 20 mm thick area with four detection bars equipment, an 80 mm area with 16 bars equipment). However, it is possible to make two successive acquisitions, doubling the field explored. In addition, the large vessels present in some pixels influence the calculations, leading to an overestimation of the VSC and therefore CBF values in these pixels.

The principle is based on the measurement of the tissue enhancement kinetics over time after bolus injection of an iodized contrast medium. Recent advances in imaging and in particular the development of multi-detector scanners have made it possible to carry out dynamic studies with temporal resolutions of the order of the second, making it possible to accurately sample the enhancement curves, particularly during the first bolus passage. Technically speaking, this involves repeated acquisitions of the same volume focused on one or more functional targets.

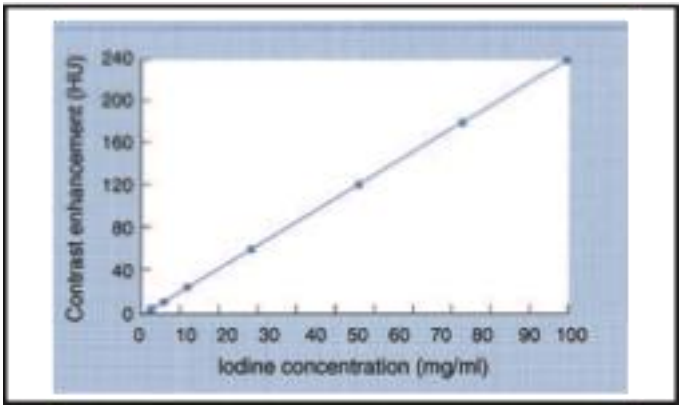
It can be integrated into the conventional morphological scanner used for extension assessment or patient monitoring. A key advantage of the scanner, unlike MRI, is the existence of excellent linearity between X-ray absorption coefficient measurements and contrast material concentration. This allows the use of simpler and more affordable mathematical models compared to MRI, where the analysis of signal enhancement is more complex.

Linearity relationship between iodine concentration and UH enhancement

Exposure to radiation is one of the limits of this modality. However, enormous progress has been made in this area, allowing a significant reduction in the doses delivered. The second limitation is represented by the potential toxicity of the injected iodinated contrast medium. The total amount of contrast medium injected is higher. However, the risk does not exceed that of a "conventional" injected CT scan.

V-2.4. Validation and reproducibility

Comparison of the perfusion scanner with the reference methods for evaluating tumor angiogenesis, radioactive microspheres. Xenon CT and H2O PET validated it for in vivo evaluation of tumor angiogenesis.



In addition, several studies have shown that there is a correlation between perfusion parameters measured by CT and histological markers of tumour angiogenesis, including MVD (microvessel density) in several types of cancer such as CHC, lung cancer and renal cell carcinoma.

V-2.5. Interests and areas of application of infusion in oncology

Changes in microvascularization parameters, in particular increased capillary permeability and perfusion, are characteristic of tumor lesions. The data provided by the infusion CT scan therefore make it possible to evoke the malignant potential of a lesion. Many studies have shown significant differences between the infusion parameters of healthy and tumor tissue but also between benign and malignant tumors; some studies also show differences in parameters between inflammatory and tumor lesion, for example to help distinguish sigmoid parietal thickening in relation to diverticulitis from thickening due to colonic neoplasia; moreover, changes in microcirculation are earlier than macroscopic morphological changes and allow earlier assessment. In some cases, the infusion study makes it possible to evaluate the aggressiveness of a tumor, to staging it, and by extension, to establish prognostic factors. For example, Assignies et al. showed a correlation between the infusion parameters of pancreatic

neuroendocrine tumors and histopronostic parameters such as the proliferation index. The use of the infusion scanner in the follow-up of patients under antiangiogenic therapy seems to be the most appropriate. This modality allows early identification of infusion changes induced by the treatment and thus to verify its effectiveness. This is the case, for example in colorectal cancer, for which Koukourakis et al have shown changes in infusion parameters on primary colorectal lesion induced by bevacizumab from day 7. Similar results were also obtained for hepatocellular carcinoma and renal carcinoma.

V-3. Other perfusion technique : MRI [30].

V-3.1. MRI perfusion

MRI is a method of imaging microcirculation sensitive to small doses of contrast media. The kinetics of contrast recording can be analyzed from T1-weighted or T2-weighted sequences*. Perfusion measurement can also be performed on non-injection sequences created using radiofrequency pulses that mark circulating blood protons (ASL sequences for Arterial Spin Labelling)

MRI data depends on the characteristics of each machine, making it difficult to compare data obtained from the same patient on different machines. Moreover, there is no directly proportional relationship between the signal obtained and the concentration of the contrast medium, by paramagnetic effect, especially at high concentration.

V-3.2 - First pass technique

Gadolinium complexes are usually used in T1 weighted imaging, for their paramagnetism property and the shortening of the T1 relaxation time they cause on the different tissues that

have captured them. These contrast agents, injected intravenously, will circulate in the vascular compartment and then diffuse to the tissue compartments by extravasation to the interstitial spaces. At the cerebral level, any intake of contrast indicates a rupture of the blood-brain barrier. To access microvascularization, magnetic susceptibility phenomena must be used. Indeed, the injection of a bolus of paramagnetic contrast agent causes a magnetic field gradient between the intravascular and extravascular spaces. The heterogeneities of magnetic field created by the presence of the contrast agent in the vessels cause a dispersion of the phases of the magnetization, inducing a decrease in the relaxation time T2*. The decrease in the observed signal (in both T2* and T2) depends on the concentration of the contrast agent in the vessel, as well as the number of vessels per unit volume, and their diameter. The injection of a contrast agent bolus, coupled with the acquisition of a dynamic series, leads to a decrease in signal strength during the first passage of the paramagnetic agent and then to a return to the initial value. In order to avoid T1 effects due to a rupture of the blood-brain barrier, and recirculation effects, the first pass curve is modelled by a "derived gamma" function.

This curve gives access to different parameters: T0 : time of arrival of the contrast medium in the section after injection ; Tc (time at peak value) : time corresponding to the maximum of the contrast variation ; TTM (average transit time) : corresponding to the width at mid-height of the curve ; CBV (cerebral blood volume) : cerebral blood volume index assessed from the integration of the surface on the curve; CBF (cerebral blood flow): index of cerebral blood flow corresponding to the CBV/TTM ratio.

- Examination protocol

The injection is carried out at the usual dosage (0.2 ml/kg) with a flow rate of 6 ml/s, concomitantly with a dynamic acquisition (15 cuts of 5 to 6 mm thick every 2 seconds), for 1 minute to 1 minute 30 minutes, usually in an axial plane. It is possible to use T2 or T2* weighted sequences to assess the magnetic susceptibility effects of the embolus. In theory, T2 spin echo sequences, more selectively sensitive to the microvascular compartment, should be chosen, but T2* sequences, although more sensitive to large vessels, are used more because of the number of possible cuts and a good signal-to-noise ratio. Care should be taken when positioning ROIs (regions of interest), to place them outside obvious vascular structures.

- Data processing and analysis

Post-processing is automated and software is offered by manufacturers, directly implemented with MRI devices. For each parameter, it is possible to obtain parametric maps, whose interest differs according to the pathology studied. Usually, all the parameters appear very interesting for ischemic pathology, whereas only the cerebral blood volume is of interest in tumor pathology. From these maps, as well as other acquired sequences, ROI are positioned in pathological and healthy areas (used as a reference) and the quantitative results are presented in the form of a ratio. For example, for tumor pathology, the maximum ratio rCBVmax = CBV tumor zone/CBV healthy zone is considered representative of the tumor. Indeed, MRI only gives access to relative measurements, because the software made available on clinical devices does not take into account the arterial input function. On the other hand, this technique allows a large number of cuts and almost the entire brain can be explored in one sequence.

- Balanced perfusion technique

This technique, which is much rarer in use, is part of clinical research protocols. It uses high molecular weight contrast agents, and vascular remanence (ultra-small iron oxide particles: USPIO). It is possible to obtain a measure of cerebral blood volume, from the contrast changes obtained between the image obtained before and after injection of contrast medium, as well as to approach the size of the tumor microvessels. In addition, these contrast agents have the particularity of having delayed capture by perilesional macrophage cells and activated microglia, making late imaging interesting.

- Spin marking

More recently, a non-invasive infusion technique has appeared in MRI, by marking arterial spins (ASL: Arterial Spin Labeling). The arterial flow upstream of the region of interest is marked (the magnetization is reversed) and, typically after a second and a half, several cuts are acquired in the volume of interest. The acquisition is repeated without marking and the subtraction of the marked - unmarked volumes allows to obtain infusion images. However, this technique suffers from a low signal-to-noise

ratio that can be improved by working at 3T. Nor does it imagery the entire brain but is very well suited for exploring stroke by marking a specific territory in a non-invasive way. Absolute infusion measurement is also possible by signal modeling.

PART TWO: THE STUDY

1-BACKGROUND

Already in 1990, the American Cancer Society estimated that 17,200 new cases of intracranial tumors were diagnosed. Some data estimate that 100,000 patients per year die from it with symptoms of intracranial metastasis. [31].

The epidemiology of cerebral tumors remains dominated by cerebral metastases followed by meningiomas, pituitary tumors and malignant gliomas in adults, when pilocytic astrocytes, embryonic tumors and malignant gliomas are most common in children. [32].

One of the strengths of brain cancer research has been the advent of targeted and anti-angiogenic therapies, which has also revealed the limitations of the RECIST 1.1 criteria [33,34].

The RECIST 1.1 [33,34]. assessment, based solely on morphological criteria, cannot be correlated in patients receiving antiangiogenic treatment, to the extent that it does not recognize the tumor devascularization induced by these treatments, which is a good sign of response to treatment without any change in size [34].

It was therefore necessary to develop new tools to assess changes within the cancer cell. PERFUSION CT(PCT), one of the latest functional imaging techniques, seems the most appropriate. Now performed in common practice, PCT remains very accessible and affordable.

Its role in the staging and therapeutic evaluation of brain tumors is well established [35].

PCT also displays cerebral flow (CBF), cerebral volume (CBV) and mean transit time (MTT). [36].

On the other side, the interest of this functional imaging technique in brain cancer comes from the fact that it could make it possible to influence therapeutic decisions and potentially reduce therapeutic toxicity by selecting patients most likely to have a better response to targeted treatment.

Several studies have already shown the ability of PCT to predict the response to bevacizumab in the case of chemo resistance (Moto Nagan et al).

In our study we try to know if the quantitative parameters of PCT could predict the effects of bevacizumab in brain cancer patients based on RECIST.1.1 guidelines

2-MATERIAL AND METHODS

2.1. **Patient selection and treatment**

- Selection of the population

Our study was carried out in the radiology department of the university hospital of TREICHVILLE. It was approved by the hospital's ethics committee, and all enrolled patients gave their written consent.

Between August 2018 and June 2019, 18 patients (11 Male, 7 Female, 47.11 middle-aged (26-68 years)) with brain tumors were recruited progressively in our study.

We included in our study all patients in whom the indication for cerebral CT for non-traumatic cause was established and in whom a stereotactic biopsy confirmed the histological type of cerebral cancer (meningioma glioma, metastasis…), then patients in whom at least one specific lesion was measurable according to RECIST 1.1(36), patients whose age was greater than 18 years, patients with adequate hematological, hepatic and renal function and no previous treatment with chemotherapy or radiotherapy.

The following are the exclusion criteria: CT scan for traumatic cause, no pathologically confirmed brain cancer (glioma, metastasis, meningioma…) and no informed consent.

The characteristics of patients and tumors are summarized in Table 1.

- Treatment plan

Patients received bevacizumab intravenously in single therapy or in association with other treatments (Table 1, figure 1). Patients were also administered corticosteroids according to clinical demand. Every 3 weeks Bevacizumab was delivered at a dose of 15 mg/Kg until the disease progressed, the patient was refused or intolerable toxicity developed.

Progression-free survival (PFS) was estimated at the beginning of antiangiogenic therapy.

Overall survival (OS) has been established from the start of anti-angio-genic therapy to death.

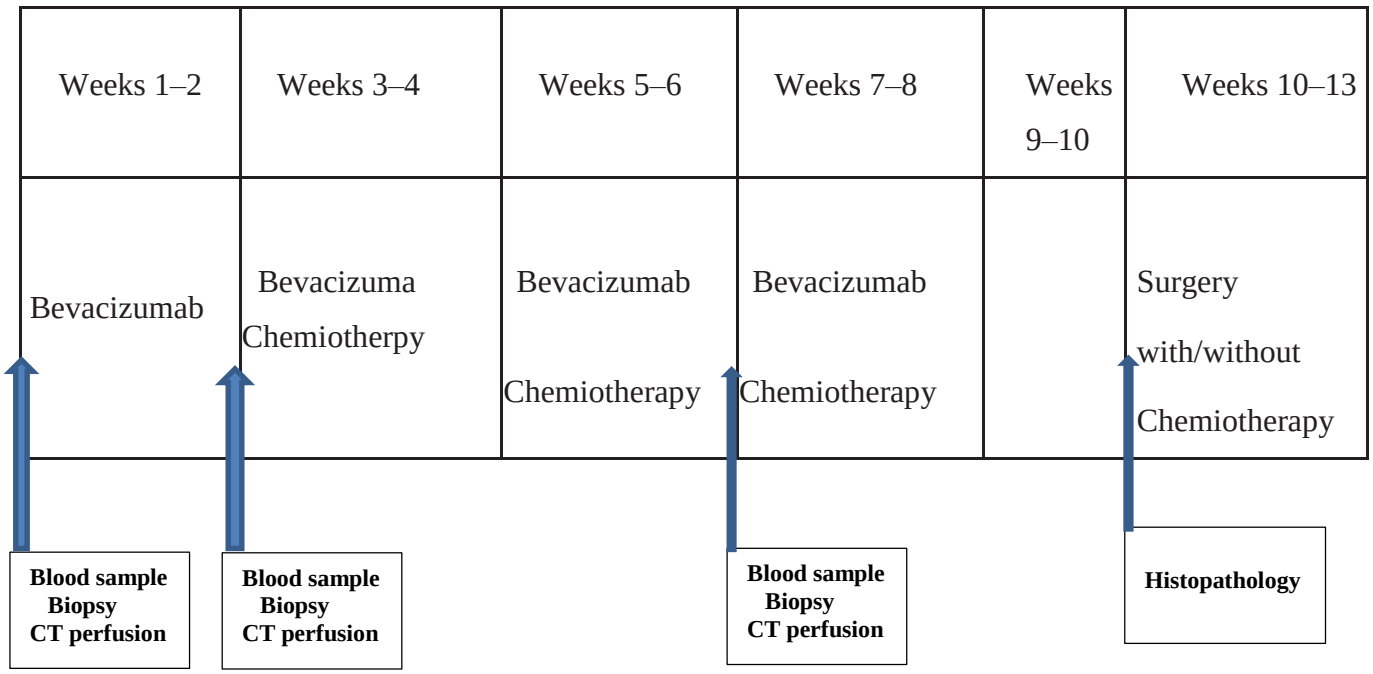
For each patient, a standard PCT was carried out before the beginning of treatment and the first dose of BEVACIZUMAB was administered on the same day.

The second PCT was completed directly before the second dose of bevacizumab, with a mean interval of 3 weeks (range 2.5 to 3.4 weeks) between the start of treatment.. (figure 1)

Radiographic responses were evaluated on PCT after each two cycles of chemotherapy according to RECIST guidelines (version 1.1) [34].

Figure.1 study design

Each patient received a single dose of bevacizumab in combination with chemotherapy for 6 months. Tumours were removed by surgery 6 to 7 weeks after the end of treatment. CT scans and blood tests were completed for treatment at both Week 2 and Week 9. Blood tests were completed prior to treatment and at Weeks 2, 6 and 9. Tumor specimens were obtained prior to treatment at week 2 and at the time of surgery.



2.2 **Response to treatment**

The primary tumor was reassessed by CT scan and histopathology 3 to 13 weeks after completion of BV. PET was not used to evaluate the responses because their cost is still very high in COTE D'IVOIRE.

The response to treatment was classified in accordance with the general rules for brain cancer and ranked as complete response (CR), partial response (PR), stable disease (SD)or progressive disease (PD). [37].

This evaluation is in accordance with a confrontation of the results of the pre- and post-BV imaging studies.

- Complete response (CR) has been defined as the disappearance of all signs and symptoms of the tumor.
- Partial response (PR) was defined as a decrease of ≥50% in tumor volume.
- Stable disease has been defined as a decrease of <50% or an increase of <25% in tumor volume.
- Progressive disease (PD)was defined as no significant change in tumor mass or an increase > 25% in tumor volume.
- Patients who had a complete or partial response were classified as clinical responders. Other patients with stable or progressive disease were classified as clinical non-responders.

Table 1. Patient tumor characteristics treated with bevacizumab

Patient N°	Sex	Age	Initial Diagnosis	Treatment BV cycle	Treatment Objectif Response	PFS (Months)	OS (months)
1	F.	26	Glioblastoma.	4	SD	2.1	5,7
2	M.	44.	Glioblastoma.	3	PR.	8.5.	12
3	M.	68.	Glioblastoma.	2	PR	8.7	13
4	F.	30.	Breast metastasis	21	SD	2.2.	3.4
5	F.	60.	Breast metastasis.	18	PD.	0,2	4
6	M	38.	Astrocytal glioma.	12	PR	5.4	8
7	F.	45.	Recurrent meningioma.	10	SD.	1.7	4.4
8	F.	58.	High-grade glioblastoma.	8	SD.	1.4	2.9
9	M.	55	Glioblastoma.	5	PR.	7	8.3
10	M	55	Glioblastoma	5.	PD	0,1	3,7
11	M.	28.	Pituitary adenoma	7.	PR	2	13
12	M.	50.	Pituitary adenoma.	7.	PR.	9	11
13	M.	60.	Glioblastoma with necrosis	14.	SD	2,1	3,8
14	M.	31	Glioblastoma	6	PR	3.7	11
15	M.	40	Glioblastoma.	8	PR	3.3	8
16	M.	36	Glioblastoma.	6	PR	3.3	10
17	F.	61.	Glioblastoma	3	SD	1.2	2,9
18	F.	69	Glioblastoma	5	SD	1.1	2,5

CR (Complet Response); PR (Partial Response); SD(Stable Diseases); PD (progressive diseases); PFS (progression free survival); OS (overall survival)

Table 2. Demographic factor in the responder and non-responder Group.

Demographic factor	Responder. (n=9)	Non-responder. (n=9)	*P* value

Age		37,77 ± 11.4	44,8 ± 22	0.637
Sex				0.391
Male		37,77 ± 11.4	±	
Female		0 ± 0	47.66 ± 19	
RECIST		48,6 ±25.0	42.7 ± 23.0	0.247
Stage				
T stage				
	1	0	2(4.8).	0.170
	2	10(27.9)	8(16.3)	
	3	11(30.6)	10(20.2)	
	4	14(38.5)	28(54.7)	
N stage	0	5(14.8)	5(10.5)	0.638
	1	4(12.19	3(6.69)	
	2	5(14.8)	9(18.2)	
	3	20(54.4).	31(60.6)	
M stage	0	2(6.8)	3(4.8)	0.829
	1a	28(75.3)	40(78.8)	
	1b	6(15.8)	8(15.4)	

2.3 **Perfusion CT (PCT)**

The acquisition was carried out on a multi-bar spiral scanner (16 bars GE MEDICAL SYSTEM).

A CT scan without injection is first performed, allowing a preliminary identification necessary for the choice of the reference level, here centered on the tumor.

The next step is the acquisition of images in dynamic mode, at the rate of four 5 mm thick joint sections each for 40 seconds (one image every two seconds), during the intravenous peripheral injection of a 40 ml bolus of nonionic iodinated contrast medium containing 300 mg Iodine /ml (Omnipaque, Nycomed, Oslo, Norway) [38,39]. at an injection rate of 4 ml/sec into a peripheral vein using an automatic injector.

The acquisition parameters are a voltage of 90 kv and an amperage of 120 ma.

The injection time is 10 seconds. The acquisition starts simultaneously with the injection and lasts 40 seconds. During this period, 80 images are acquired, i.e. 20 images for each of the 4 cutting levels, with a rate of one image every 2 seconds. This protocol therefore makes it possible to obtain four 5 mm thick cerebral CT cuts, i.e. a volume of 20 mm. When reconstructing the data, two 10 mm volumes can be obtained, which improves the signal.

Patients were dosed with the total effective dose corresponding to 1.1 msv as reported in the literature. [38,40] calculated by CT Patient Dosimetry Calculator impact (v. 0.99×, Medical Devices Agency, London).

2.4 **Image analysis**

By comparing the baseline studies with the best response obtained during BV, patients were divided into two groups: non-respondents (complete response (CR) or partial response (PR) based on RECIST) and non-respondents (stable disease (SD) or progressive disease (PD) based on RECIST).

The perfusion database was uploaded to an image processing console workstation and analyzed using software (CT Perfusion 3.0; GE Medical Systems),The parameters generated by the software were cerebral blood flow (CBF in ml per 100 g wet tissue per minute), Cerebral blood volume (CBV in ml per 100 g wet tissue), mean transit time and an optional set including Mean Perfusion, Peak Enhancement, Time to Start, Permeability (PS = permeability surface product in ml per 100 g wet tissue per minute).

The perfusion can be determined using the maximum slope of the tissue concentration curve as a function of time or its peak height, normalized to the arterial input function [41]. a double-compartment model (intravascular equivalent to blood and extravascular equivalent to tissue extracellular fluid) is used by supposing that the reflux of contrast medium from extravascular to intravascular compartments is negligible for the first 1 to 2 minutes (technique called Patlak analysis [42].

For the evaluation of perfusion images, two independent radiologists, who concealed patient identity and clinical history, reviewed and analyzed all perfusion studies.

Decisions on the results of PCT were made by consensus.

The anterior cerebral artery (ACA) or the middle cerebral artery (MCA) was chosen as the entry artery, and a large venous structure, such as tortuous herophilia, is chosen as the entry artery. Special regard was given to the selection of arterial and venous input features and the setting of limit values for unenhanced and enhanced images. To avoid partial volume effects, a suitable large and orthogonal reference vessel to the scanning section has been selected. The ROI was drawn by a free hand, incorporating the part as much as possible. Great caution had been taken to prevent interference with tumor margins in order to avoid peritumor hyperemia.

For the quantitative study, the complete volume of interest (VOI) of the target lesions was extracted by semi-automatic segmentation. If the segmented edge of the target lesion was incorrect, the reviewers hand-rectified the VOI for the edge of the target lesion on the slices, including the target lesion on the monochromatic 70 kev axial images. After a VOI covering the entire target lesion was drawn, the segmented VOI of the entire target lesion was propagated to the other two image modes to cover the same VOI of the target lesion on all three images. Mean CT attenuation densities of all target lesions in post-contrast CT images (70kev monochromatic CT images) were measured. The average iodine concentration (mg/ml) for the same VOI covering the entire target lesion was also measured in iodized images.

The size of the tumor was defined by the longest diameter of the tumor on the axial images. The TNM stage (7th edition) was determined based on radiological results, with the help of histopathological results [36,38]. The average of the values measured by two independent radiologists was used for the final analysis.

2.5 **Statistical analysis**

Routine tumor CT perfusion and RECIST measures were matched against the results obtained two weeks after bevacizumab treatment and after the end of bevacizumab treatment and chemotherapy by using the Student t-test, for the purpose of matching the two sets of data.

The continuous variables were expressed as means and standard deviations.

Chi-square test or Fisher exact test were used to compare perfusion parameters before taking BV between clinical respondents and non-respondents.

The univariate survival study was carried out by using the long-range logarithm test. The statistically significant results of the univariate analysis were then included in the multivariate analysis.

The effect of blood flow and clinicopathological variables on survival was measured using the proportional risk of the Cox model.

A logistic regression model was also used to evaluate the predictive factors of BV responses

The survival curves were estimated by the Kaplan Meier method. The p-values were also estimated for each comparison. $P<0.05$ indicates a statistically significant difference.

The $p < 0.05$ values were considered statistically significant.

All statistical analyses were performed using commercial software (SAS software, system release 8.2 and Microsoft Excel 2013).

3-RESULTS

3.1 Patient characteristics

The characteristics of the eighteen patients treated by BV are summarized in Table1
The PCT allowed us to establish the t and n stages according to RECIST 1.1

- Response to treatment and prognosis.

We observed complete and partial responses in (n=9 And 50%) patients and no response in patients (n=9 And 50%)
The respondent group had considerably better survival than the non-respondent group(p=0.007)

3.2 Results of PCT

Qualitative and quantitative measurements were made on the reference PCT images, and the results were compared between the responder and non-responder groups (Table 2)

- Pre-BV PCT parameters: clinical responders and non-responders.

Considerable differences were observed between the respondents and non-respondents groups:
-the pre-BV blood flow rate (p = 0.0002),
-the pre-BV average transit time (p = 0.001) and
-the pre-BV blood volume (p = 0.01).
Thus, patients with high initial blood flow, short mean initial transit time or high initial blood volume prior to initiating treatment with BV showed a good response to initial BV blood flow (Figure 2), long mean initial transit time or low initial blood volume,
On the other hand, the non-responders to BV processing initially had the opposite parameters.
The permeability surface product was not considered statistically significant (Table 4).

- Comparison of Imaging Biomarkers at 2 Weeks After Bevacizumab Therapy

This study wanted to know if there was an early change between pre-BV perfusion parameters and 2 weeks BV treatment in PCT parameters.

Two (2) weeks after treatment with bevacizumab, considerable reduction in tumor blood volume (mean change: 31.9%, 2.95 ± 3.1 vs 1.6 ± 1.8 mL/100 g, p = 0.01) and a measurable reduction in blood flow (48.1 ± 39 vs 35.3 ± 40.0 mL/100 g/min, p = 0.1) and permeability (11.2 ± 10.4 vs 8.4 ± 6.6 mL/100 g/min, p = 0.1) was recorded (Table 3). Tumor size did not show substantial change (7.1 ± 3.3 vs 7 ± 3.5 cm, p = 0.24).

Table 3. Early Tumour Response by Perfusion CT

CT Perfusion Parameter	Pretreatment BV	At Week 2[a]	*P*	Posttreatment[b] BV	*P*
Blood flow (ml/100 g/min)	48.1 ± 40	35.3 ± 39.0	0.1	27.9 ± 33.0	0.0005
Blood volume (ml/100 g)	2.95 ± 3.1	1.6 ± 1.8	0.01	1.35 ± 1.2	0.001
MTT (s)	9.0± 3.1	8.4 ± 2.4	0.47	9.4 ± 3.9	0.5
Permeability surface area product (mL/100 g/min)	11.2 ± 10.4	8.4 ± 6.6	0.1	4.3 ± 3.9	0.005
Tumour size (cm)	7.1 ± 3.3	7.0 ± 3.5	0.3	7.7 ± 4.4	0.24

Note— Unless the contrary is specified, data are mean ± SD. A p value of < 0.05 indicates a significant difference between baseline and post antiangiogenic treatment values. MTT = mean transit time.

[a] Indicates 2 weeks after the initiation of bevacizumab treatment.

[b] indicates after the administration of bevacizumab and chemotherapy.

3.3 Predictive factors for bevacizumab responses

A statistical regression test was undertaken to pick out predictive factors independent of the BV response (Table 5).

- Prediction of the response of the treatment to BV by the pre-BV blood flow.

A very significant difference was found for pre-BV blood flow between clinical and non-respondent. For example, for pre-BV blood flow, when the threshold was set at 50 ml/100 g/min, the accuracy was 80.3%, the sensitivity was 80.5% and the specificity was 80.0% for the detection of clinical responders (Table 4).

Table 4. Perfusion parameters in clinical responders and non-responders

Perfusion parameter.	Responders(n=9).	Non-responders(n=9).	*Pvalue*
Blood flow(ml/100g/min)	71.6 ± 38.3	45.1 ± 15.7	0.01
Blood volume (mg/100g)	4.3 ± 2.3	2.7 ± 1.4	0.05
Mean transit time (sec)	9.2 ± 3.3	8.7 ± 3.1	0.8
Permeability-surface (ml/100g/min).	14.6 ± 12.2	8.2 ± 8.1	0.1
Tumor size	4.8 ± 2	8.7 ± 4.1	0.05

Note -only for *p*, data are mean SD. MTT=mean transitime. A p value of <0.05 indicates a significant difference in the baseline and value between good responders and poor responder

- Prognostic relevance and multivariate analysis.

Using univariate analysis, blood flow has demonstrated a meaningful relationship with survival (p=0.006) (Table 5). The combination of other clinico-pathological factors, such as age, tumor type, t-stage, n-stage, tumor size and the treatment were inconsiderable. Blood flow, stage t, stage n and tumor size were used in the COX regression model to determine the unaffiliated prognostic value of various patient survival parameters (Table 5).

It was therefore established by consensus that,

- blood flow was a predictive factor (p = 0.01; risk ratio, 2.30; 95% IC, 0.18-11.58).

Patients with high blood flow tumors (≥50 ml/100 g/min) survived significantly longer than those with low blood flow tumors (<50 ml/100 g/min) (p=0.007).

Table 5. Logistic regression analyzes of predictive factors for responders

Variable	odds ratio.	95% CI for OR.	*P* Value
Univariate analysis			
Blood flow <50 vs50mg100g/min	2.30	0.18-11.58	0.01
Age	0.892	0.859-0.026	0.633
T stage	0.711	0.206-0.19	0.571
N stage	0.546	0.082-1.259	0.95
Tumor size <80mm vs80mm	3.813	0.299-31.732	0.332
Multivariate analysis			
Blood flow	5.18	0.48-22.68	0.006
T stage	0.44	0.24-4.64	0.52
N stage	1.73	0.17-17.58	0.41
Tumor size	0.59	0.13-1.51	0.41

4- **DISCUSSION**

This study was conceived to find out if the quantitative parameters of baseline PCT could predict the effects of BV in patients with brain neoplasms.

Brain CT is an imaging modality employed for diagnosis and staging purposes of brain tumors, it can be a tool to determine early biomarkers to allow an appropriate therapeutic strategy. The use of imaging biomarkers to assess treatment response could be an important non-invasive tool to better distinguish the patients most eligible for these treatments.

Previous studies had already shown the role of PCT in monitoring treatment response after ischemic stroke.

More recently, additional studies have demonstrated that PCT parameters can be used for prognosis and prediction of early tumor response to NSCLC treatment [43,44].

Thus, in view of its results, we assumed from the outset that the PCT parameters could also predict the Response to BV as monotherapy or in combination.

After only a first dose of BV, significant reductions in CBV were observed in the overall patient population. From the analysis of each patient (Table3), it can be seen that the average CBV after BV treatment tends to approach the value 1, which represents the average CBV of normal-looking brain tissue.

The standard deviation also decreased significantly after the first round of BV, suggesting a finer distribution of CBV values in the lesion, consistent with a reduction in vascular heterogeneity of the tumor, as shown by perfusion cards obtained during treatment.

These data suggest that a raised initial perfusion may reflect a decrease in antiangiogenic agent activity, although this tendency should be corroborated by more sophisticated studies in a larger patient population.

Thus, our study showed that tumors with higher blood flow, higher blood volume or shorter mean transit time may have a better clinical response to BV. For BV blood flow, the accuracy was 90.2% for detection of clinical responses if the threshold was set at 50 ml/100 g/min. We

found that patients with high blood flow tumors outlived significantly longer than those with low blood flow tumours. Hermans et al [45] indicated similar results and confirmed that a low rate of perfusion rate predicted a low response to radiation therapy.

All this result may be linked to the oxygenation of the tissues and tumor microcirculation. It has been established that tissue oxygenation is a very strong factor of radio sensitivity, both in vitro and in vivo [46,47]. The administration of oxygen to the tumor tissues seem to be based on a microvessel network, focusing on in vivo vascular findings and blood flow in tumor microcirculation. It is no longer a secret that oxygen gradients exist in microcirculation, and it has already been accepted that microvascular pathways with higher flow rates have a higher oxygen content [48].

In addition, Hemphill et al [49] reported a significant link between the local oxygen tension of brain tissue and the average transit time, i.e., the intraparenchymal oxygen tension of brain tissue was negative and significantly correlated with the average transit time.

On the other hand, tumor microcirculation is certainly a significant factor in the administration of the drug to cancer cells. The effectiveness of the drug administration may be important in highly vascularized tumors.

Thus, PCT has the ability to reveal microvessel density and tissue oxygenation status. These facts confirm that Perfusion parameters will be positive predictive and prognostic factors in patients who have been treated with BV associated or not with chemotherapy
While it is true that PCT reflects tissue oxygenation, it is also true that anti-VEGF therapies play an important role in this tissue oxygenation by induced hypoxia ([50,51,52].
Preclinical research has assessed the role of bevacizumab in on intratumoral oxygenation status in mice, allowing the differential between acute hypoxia and chronic hypoxia resulting from limited infusion and limited diffusion of oxygen (54). The instigators, Masunaga et al [51], said that bevacizumab preferably oxygenated the acute hypoxic fraction (HF) instead of the chronic HF of the tumor. Thus, the leftover HF after antiangiogenic treatment should preferably be composed of a population of cells rich in chronic hypoxia, whose control has been shown to have a significant impact on local tumor control.

It can be argued that evidence of an increase in necrotic areas on the side of the lesion during treatment should represent an initial sign of treatment failure, because of the lack of local control of the tumor.

To go further, Hattingen et al [50] examined in the case of recurrent glioblastoma, if bevacizumab has changed the metabolism of oxygen and energy and provided antitumor.However, the authors said that this long-term hypoxia does not appear to promote more aggressive tumor growth, as no link has been established between T2 reduction and a shorter duration of OS.

The controversial promising outcome of BV has been reported recently by Keunen et al[53]. A set of data suggesting that vascular modification induced by anti-VEGF therapy may induce a more hypoxic tumor microenvironment that will induce an increased invasion of tumor cells in the normal brain. studies combining imaging and molecular biomarkers will likely provide in the near future a deeper understanding of the complex cellular mechanisms by which BEVACIZUMAB temporarily corrects the abnormal vascular system of tumors. [54,52].

There are limits to our study. As very often with the cerebral PCT, there are limits to our study. The 4 cm coverage of PCT in the cranio-caudal direction prevented us from showing the full tumor volume in some patients and, in these cases, only the central part of the lesion was examined. Because of the insufficient statistical strength of the patient group analyzed, some correlations were found between the observed changes in perfusion and clinical parameters.

Other studies are necessary, particularly those involving more patients, to better explore the interconnections between proposed perfusion parameters and clinical outcomes.

Due to the short duration of the scan (45 s), perfusion and blood volume are the most accurate maps; in fact, a vascular permeability study as suggested by Miles et al [55], should have required a scan time of 2 to 10 min.

Some parameters did not show the expected predictive power because they showed high standard deviations due to the heterogeneity of the tumor.

The presence of necrotic tissue within the lesion, especially in high-grade gliomas and large metastases, surely affects the data, decreasing the mean values of blood volume, flow and permeability. In addition, it should not be forgotten that the PCT has several disadvantages, as suggested by Miles et al [55], such as variability in measurement due to technical and biological causes. [56,57]

5-**CONCLUSION**

This study shows the evidence of effectiveness in quantifying variations in the overall distribution of IVC values in the tumor. The improvement in hypoxia after a single dose of bevacizumab was a predictor of a greater reduction in tumor volume.

It shows the possibility that CT perfusion can predict the response to BV in treatable brain tumors. This could lead to the choice of the optimal therapeutic strategy for the treatment of brain cancer.

In the near future, we may be able to determine q

But in order to obtain more convincing results, a larger number of patients are required to be studied

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