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Brain Metastases: Biology and Comprehensive Strategy from Radiotherapy to Metabolic Inhibitors and Hyperthermia

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1. Introduction

Metastases to the brain is one of the most feared complication of systemic cancer and its incidence is rising for several reasons. The two most important reasons are the improvement in treatment, with a longer patient life; and the advance in diagnostic and imaging means Magnetic Resonance Image (MRI) and Computed Tomography (CT), Positron Emission Tomography [PET]) that have permitted to detect smaller lesions in asymptomatic patients. These improvement in radiology allows earlier diagnosis and result in better treatment management (Kamar et al., 2010, Rao et al, 2007, Patchell et al. 2003). Single metastases are detected in greater proportion. For example, in the case of ovarian tumors brain metastases are solitary in 43% of the cases (Pectasides et al. 2006). Single metastases appear approximately in one quarter of all patients with brain metastases (Rao et al. 2007). Norden et al. 2005 recently reported that breast, colon and renal cell carcinoma tend to produce single metastases, whereas melanoma and lung cancer have a greater tendency to produce multiple metastases. Single metastases can be treated surgically or by high precise radiotherapy modalities such as Gamma knife and StereoTactic Radiotherapy (SRT) or Conformal Radiotherapy (CRT). SRT was initially used for substituting surgical approach in patients with inaccessible tumor location or with comorbid medical conditions, now is used in many institutions as first approach, peculiarly from breast colon and renal carcinoma. Actually, many patients, refuse surgical approach so the use of SRT or CRT in combination with whole brain irradiation (WBRT) or SRT as a boosting method after WBRT is increasing. Associated to radiotherapy and chemotherapy we suggest and discuss the biological reasons for adding hyperthermia and glycolysis metabolic inhibitors with the aim to obtain a better control of brain metastases.

2. Epidemiology, pathology and prognosis of patients with brain metastasis

Brain metastases occur in 20% to 40% of cancer patients. Posner and Chernik, from 1970 to 1976 at the Memorial Sloan-Kettering Cancer Center, autopsied 3219 cancer patients. They found that 24% of these patients had intracranial metastases and the 20% had leptomeningeal metastases (Posner and Chernik 1978). Other studies reported similar percentage even if the methodology is slightly different (Baker et al. 1942, Chason et al 1963, Nussbaum 1996). In decreasing frequency, lung cancer, unknown primary, breast, melanoma, renal, and colon cancers are the most common tumors to metastasize to the brain (Pectasides et al. 2006, Norden et al. 2005, Posner and Chernic 1978, Chason et al 1963, Nussbaum et al. 1996).

2.1 Localization of brain metastases

Another important aspect is the precise localization of the metastases in the brain (Globus et al. 1942, Tom et al. 1946, Zimm et al. 1981, Tikhtman et al 1995). Approximately the 80% of metastases are localized in the cerebral hemisphere, 17% in the cerebellum and 3% in the brain stem (Tikhtman et al 1995). Delattre and contributors have also analyzed the localization of metastases in the specific regions of the cerebral hemisphere (Delattre et al. 1988). They found that brain metastases involved the frontal area for 21%, the parietal and the temporoparietal-occipital for 19%. These authors have also outlined that metastasis located preferentially at the junction of gray and white matter. Hwang et al. recently reexamined the importance of the vascular border zone and the gray and white matter junction in the distribution of brain metastases and agreed with Delattre and contributors (Hwang et al. 1988). They found in 302 metastatic brain lesions studied, that gray and white matter junction was the preferred site for 64 % of the brain metastases and the vascular border zones were the site of predilection for the 62%. These results support the notion that metastatic emboli tend to lodge in an area of sudden reduction of vascular caliber (gray/white matter junction) and in the most distal vascular field area (Border zone) (Hwang et al. 1988).

2.2 Shape of brain metastases

Most metastases appear round well-demarcated lesions that displace rather than invade the surrounding brain parenchyma. The lesions can vary in size ranging from microscopic to masses of 1-4 centimeters in diameter. The histopathologic features are similar to that of tumor of origin.

Microinvasion is present although the majority of metastatic lesions appear well demarcated and sometimes with reactive astrocytosis surrounding the metastatic area (Shaffrey et al. 2004). A new vasculature can appear at peripheral zones and is part of the edema. In central areas, necrotic areas are present (Nathoo et al. 2005). Meningeal metastases diffuse into the subarachnoid space with accumulation around blood vessels (Shaffrey et al. 2004).

2.3 Prognosis of brain metastases

Untreated brain metastases have a dismal prognosis, generally no greater than 1-5 months. Gaspar et al. 2000, studying a RTOG (Radiation Therapy Oncology Group) data base, performed a Recursive – Partitioning Analysis [RPA] on 1200 patients. They identified the factors able to influence the prognosis of these patients (Gaspar et al. 2000, D'Ambrosio et al. 2007). Among the several prognostic factors, Karnofsky Performance Status (KPS) has been

identified as the most important. The other important factors were: status of primary tumor, age and the presence or absence of systemic metastases. Stratifying the patients according these criteria they have been able to obtain the following prognostic factors. Patients with KPS = 70%, with age = 65 with controlled primary tumor and absence of systemic metastases had a median survival of 7.1 months, whereas the survival was reduced to 2.3 months for patients with KPS < 70. The presence of uncontrolled tumor and systemic metastases even if with a KPS = 70% reduced the median survival to 4.2 months (Gaspar et al. 1997, 2000). The survival was not different between patients with undiagnosed primary lesion and thosewith diagnosed primary tumor (6 and 4.5 months, respectively; p = 0.097) as reported in a recent study by D'Ambrosio (D'Ambrosio et al. 2007).

2.4 Brain metastases biology

Researchers have gained insight into the mechanisms by which metastatic cells arise from certain primary tumors (i.e. breast, melanoma) and metastasize to brain. These findings have been obtained in a mouse model (Kang et al. 2004, Nicolson 1993, Beasley et al. 2011). These authors have outlined that metastases formation are not due to patterns of initial cell arrest, motility, or invasiveness, but rather to the ability of metastatic tumor cells to grow in that environment, this in agreement with the Paget hypothesis of seed and soil. In other words, the formation of metastasis requires the right cells with the compatible environment (Fidler 2002, 2010, Deichman 1998).

Metastatic process is a high selective non-random process consisting in a series of linked sequential steps. In a heterogeneous population of primitive tumor cells only some are able to survive and to lodge at distant sites (Shaffrey et al. 2004). The outcome of cancer metastases depends on multiple interactions between metastatic cells and homeostatic mechanisms. Each metastatic step is selective and if the various steps are not completed, the metastatic process may fail. This is probably why only 0.01% of the cells that reach the circulation form a metastatic colony (Shaffrey et al. 2004, Kang et al 2004).

For tutorial purpose we can divide the metastatic process to the brain in the following steps (Fidler 2010, Deichman 1998):

A) process of selection among the heterogeneous tumor cells of origin into an aggressive and able to mobilize subpopulation; B) penetration of this selected subpopulation into the host circulation; C) localization into the microvasculature of the brain; D) crossing of Blood Brain Barrier (BBB); D) migration and growth in the brain structure.

The process of selection (A) is the result of different pressures exerted by the tumor microenvironment and the genetic instability intrinsic to the tumor cells living in that environment. For different pressures we intend: tumor hypoxia, different metabolic advantageous tumor micro-area, immunologic pressure, presence or absence of an angiogenesis process. These different pressures can select among cells genetically unstable, cells able to survive in a different environment, to mobilize and to reach the blood stream (Deichman 1998). To gain access to the general circulation and to colonize to distant organs metastatic cells must invade tumor associated vasculature. The molecular mechanisms controlling the penetration of blood vessels are not completely understood (Beasley et al 2011, Fidler 2002, 2010, Deichman 1998). Once these cells have reached the blood vessels, various mechanisms are needed to survive both the immune system and the shear stress. To avoid the identification the immune cells, metastatic cells shielded under an agglomerate of platelets and red blood cells (Deichman 1998)]. Other important mechanisms are the resistances by metastatic cells to the apoptotic effects of reactive oxygen radicals produced

by macrophages and neutrophils and the production of prostaglandins of E type (Fidler 2002). Furthermore the adhesion of the platelets on the metastatic cells induces a hypercoagulable state that increases the metastatic potential. In fact this adhesion increases the resistance to both the immune system and the shear stress (Kehrli 1999).

The most common metastatization to brain occurs by hematogenous route. One route is via the general circulation. In fact in the resting state, the brain receives 15% to 20% of the body's blood flow, thus making it likely that circulating tumor cells will reach the brain. The second, via the vertebral venous system (Batson's plexus) which explains the absence of lung metastases found in certain patients with lung cancer. This spreading way is disputed and not confirmed by all authors (Deeken et al. 2007).

Once metastatic cells have survived the circulatory stream, they may adhere to the endothelium, extravasate into the organ and then begin to proliferate in the new parenchyma. The arrest in the microcirculatory system is regulated by several factors, among them the multiple vascular adhesion molecules and the size of circulating emboli. Among adhesion molecules two families seem to be implicated: the selectins and the products of Immunoglobulin (Ig) genes and the integrins (Deeken et al. 2007). Integrins are major adhesion and signaling receptors that mediate cell migration and invasion (Shaffrey et al. 2004). In the case of human non small lung cancer (NSLC) the block of adhesion molecules integrin $\alpha 3\beta 1$ has been demonstrated to significantly decrease the brain metastasis (Nathoo et al 2005).

After reaching the brain capillaries, the metastatic cells must cross the BBB, degrade the brain Extracellular Matrix (ECM) and invade the brain parenchyma. This interaction is tight regulated by the paracrine and autocrine growth mechanisms present in the brain (Nicolson 1993). BBB is constituted by brain endothelial cells associated with pericytes and astrocyte foot processes. Brain endothelial cells have continuous tight junction, no fenestrations and is highly selective in its permeability (Perides et al. 2006). In experimental melanoma the fibrinolytic system facilitates tumor cell migration across the BBB as demonstrated by Perides and his group (Perides et al. 2006). For metastasis to the brain from breast tumor, the cooperation between metastatic cells and astrocyte is of importance (Weil et al. 2005).

To determine why certain tumors produce site-specific metastases to the brain, Fidler and collaborators studied cellsfrom K-175 melanoma syngeneic to C3H/HeN mice and the B16 melanoma syngeneic to C57 Bl/6 mice (Fidler 1999, 2002, 2007). Regardless of the route of injection (internal carotid arteries-or directly into the cerebrum) K-175 produced melanocytic metastases in the brain parenchyma, whereas B16 cells produced lesions in the meninges and ventricles. These researches tried to understand which factors were responsible for the growth the melanoma cells in the specific areas (brain parenchyma, meninges). Some important aspects have been elucidated. For example B16 cells did not produce measurable gelatinase A activity whereas K- 175 cells did. The presence of gelatinase theoretically can facilitate cells extravasation and the growth into the parenchyma. However studies with hybrids of B16 and K-1735 able to produce gelatinase A, failed to grow into brain parenchyma. Fidler switched his research on the different growth factors present in the brain. He studied growth factors such as Epidermal Growth Factor (EGF), basic Fibroblast Growth Factor (bFGF), Platelet Derived Growth Factor (PDGF), however only Transforming Growth Factor-beta 2 (TGF-β_2)showed a greater concentration in the brain and was able to inhibit the growth of B16 and B16/K-1735 hybrid cells explaining the incapacity of these hybrids in producing intraparenchymal brain metastases (Fidler 1999).

Whether the progressive growth of brain metastases depends on neovascularisation is also unclear. As outlined by Bucana: "immunohistochemical and morphometric analyses show that the density of blood vessels within experimental metastases in the brains of nude mice, or within brain metastases derived from human lung cancer, is lower than in the adjacent, tumor-free brain parenchyma. However, blood vessels associated with brain metastases are dilated and contain many dividing endothelial cells. Immunohistochemical analysis also reveals that tumor cells located less than 100 micrometer from a blood vessel are viable, whereas more distant tumor cells undergo apoptosis. The blood-brain barrier is intact in and around experimental brain metastases smaller than 0.25 mm in diameter, but is leaky in larger metastases "(Bucana et al. 1999). Regarding melanoma other authors have found that neurotrophins (NTs) can promote brain metastases. NTs enhance the production of ECM degradation enzymes such as heparanases. Heparanases do not only degrade ECM but also the basement membrane of BBB Nathoo et al 2005, Menter et al 1994, Marchetti et al 2003, Denkins et al. 2004).

The potential of angiogenesis in breast metastases has been further been studied. VEGF has been reported to increase the penetration of metastatic MDA-MB-231 breast carcinoma and to play a role in brain metastases dormancy in the absence of inhibitory antiangiogenic factors (Kim et al. 2004, Santarelli et al 2007, Palmieri et al. 2007, Yano et al,. 2000, Kaplan et al. 2005, Chen et al. 2007). Yano and collaborators however do not agree regarding the importance of VEGF on brain metastases and in an experimental mouse model using six different human cancer cell lines has reported that VEGF expression was necessary but not sufficient for the production of brain metastasis (Yano et al. 2000).

Recently, the idea of premetastatic niche is leading the way (Kaplan et al 2006). Some authors support that the arrival of bone marrow-derived hematopoietic progenitors cells in distant sites represent early changes in the local environment (premetastatic niche) that dictates the pattern of metastatic spread and explains tumor dormancy (Kaplan et al. 2005,2006). Santarelli et al. 2007, outline that the reactive monocytosis and activated microglia present in the premetastatic niche increase the local inflammatory response and can induce the growth of tumor cells transplanted to the brain. Furthermore these authors outline that it is plausible that the brain is able to generate the adequate environment in anticipation and preparation of the ensuing metastatic colonization (Santarelli et al. 2007). Other studies have evidenced new mechanistic insights regarding some kind of tumors such as breast cancer and melanoma.

Her-2 receptor. Overexpression of Her-2 receptor in breast carcinoma seems not only correlated to a poor prognosis but also to an increased colonization to the brain as demonstrated by Palmieri et al. (2007).

Metabolic factors. Regarding only breast carcinoma, Chen et al (2007) have evidenced by proteomic analysis, that brain- metastasizing cancer cells over expressed enzymes involved in aerobic glycolysis and tricarboxylic acid cycle (TCA) cycle. From this study the authors outline that breast cancer that colonize the brain are able to adapt to the energy metabolism of the brain or develop metabolism able to survive in that specific environment.

Stat3. In melanoma, the activation and over expression of Stat3 (Signal Transducer and Activator of Transcription 3), as reported by Tong-Xin is associated to brain metastases and might be considered a new potential target in this clinical situation (Tong et al 2006).

Metastasis suppressor genes. Recently seven Metastasis Suppressor Genes (MSGs) have been identified. These genes have no effect on the growth of primary tumors but have the

ability to suppress metastases *in vivo*. Proteins that regulate different functions such as adhesion, migration, growth and differentiation are coded by these MSGs. These genes have been described for breast carcinoma (Seraj et al. 2000), melanoma (Leone et al. 1991) and prostate cancer (Dong et al. 1995).
Notwithstanding all these progresses the entire process of brain colonization remains actually poorly understood and better human and animal models are to be tried. It is our hypothesis that the peculiar metabolism of the normal brain with its high glucose uptake may explain the large incidence of metastases.

3. Current methods of treatment of brain metastases

The treatment of brain metastasis is multidisciplinary and different medical (surgeons, radiotherapists, chemotherapists) and non-medical figures (specialized nurses, health physicists, and radiotherapy technics) are interested. The clinical treatment consists in a combination of surgery, radiotherapy and chemotherapy.
For describing the current therapies of brain metastases we have followed the suggestions of the "American College of Surgical oncology CNS Working Group" (2005) and some recent reviews on the argument (Shaffrey et al. 2004, Eichler A. F. and Loeffler J. S 2007, Ngguyen and De Angelis 2004). The criteria used by the American college of Surgical Oncology are the following: age, Karnofsky Index, presence or absence of non-Central Nervous System (CNS) metastasis. Using these criteria and the predictive study [RPA] of Gaspar et al. (1997, 2000) it is possible to calculate the median survival. For patients falling in the RPA 1 with median survival = 7.1 months, an aggressive approach is suggested. It is out of doubt that the improvement in imaging techniques has changed the treatment options, and that the survival of patients with brain metastasis is dependent on the status of their systemic disease (Kamar et al. 2010, Rao et al. 2007, Patchell 2003, Eichler A. F. and Loeffler J. S 2007).

3.1 Surgery

Surgical approach has changed the survival and the quality of life of many patients. The most convincing evidence of this benefit is reported for Non-Small Lung Cancer (NSLC) patients with a single brain metastasis. Different authors have reported a 5-years survival ranging from 0% to 45% (Hankins et al. 1988, Wronski et al. 1995). As outlined by Nguyen and De Angelis (2004) this variation on survival is accounted by two factors: a) variation on treatment aggressiveness of primary lung tumor, b) variation on the incidence of systemic disease burden among those series.
Surgical resection is generally followed by Whole - Brain Radiation Therapy (WBRT). WBRT has demonstrated palliation of neurologic symptoms and extension on survival (see studies of Patchell et al. 1990 and Vecht et al. 1993). Surgery for single metastases has shown benefit for melanoma (Buchsbaum et al. 2002), prostate cancer (McCutcheon et al. 1999), colorectal cancer (Hammoud et al. 1996), ovarian (Cormio et al. 2003) and cervical cancer (Tajran et al. 2003).
Surgery for multiple brain metastases is a relatively new approach supported by the important retrospective study of University of Texas M.D. Anderson Cancer Center. In this study were treated 56 patients with no more than 3 metastases. No more than 3 craniotomies were performed and the group was divided in two subgroups according to the extension of the surgical resection. For one group [A] of 30 patients the complete resection was not possible, for a second group [B] of 26 patients the multiple metastases were completely

resected. In a third Group [C], 26 patients were resected for single metastasis and this group was used as control. From the comparison of the various subgroups the following results emerged: Group C and Group B obtained the same survival time and a multivariate analysis demonstrated that the only variables significantly affecting the survival were the groups of patients and the extent of the primary tumor (Bindal et al. 1993). The recurrence was similar in group B and C suggesting that an aggressive surgical approach may be useful. This approach has been confirmed by another study on 138 patients (Iwadate et al 2000). This study included other two variables: age and Karnofsky index. Age >60 years and Karnofsky < 70 and incomplete removal were significant factors.

3.2 Radiation therapy

Radiotherapy is the mainstay therapy of brain metastases. Currently there are three major categories of radio therapeutic treatments of brain metastasis: WBRT, radiosurgery, stereotactic radiotherapy. There are two options for radiosurgery: Gamma knife, Linac – based radiosurgery.

WBRT has been demonstrated by Patchell 1990 and Vecht 1993 to increase life survival in association with surgery. The WBRT is a palliative procedure which aim is to achieve life prolongation, local control and improvement in quality of life. WBRT has been also used prophylactically, aimed to treat malignancies having high brain metastasizing affinity, such as small cell lung carcinoma (SCLC), leukemia and lymphoma (Meert et al. 2001, Brown et al. 2005). The most frequently applied doses range from 20 Gy to 30 Gy in 5-10 sessions. Doses from 30 to 36 Gy are used as prophylaxis in the case of SLC and from 12-18 for hematologic diseases (Alexander et al. 1995, Brown et al. 2005). The combination of WBRT with radiosurgery will be discussed later.

Radiosurgery is now possible because of the availability of CT and MRI and computer planning makes possible the delivery of high dose of radiation to a precise target tumor area. This delivering of precise high dose of radiation energy to a tumor is called radiosurgery. It can be achieved combining 3 elements: 1) stereotactic localization of metastatic lesion; 2) precise collimation of the radiation energy and 3) administration of the total dose coming from different points in space and intersected in a single target volume. The peculiarity of radiosurgery is the fall of dose at the target edges, this permit to concentrate the dose to the target tumor area sparing everything possible the healthy tissue surrounding the tumor (Lunsford et al. 1990). Two radiosurgical treatment facilities exist: **Gamma Knife**, **Linac radiosurgery**.

Historically, LeKsell in Sweden was the first to apply radiosurgery. Initially low energy x-rays (280 kV) were used and concentrated stereotactically to the intracranial target. The technique was first accepted with skepticism; however after the initial studies by Lunsford et al. (1990) (University of Pittsburgh), radiosurgery has gained a considerable acceptance. Lately in 1967, Leksell, in collaboration with Larsson, developed according to the same principle of radiosurgery the first cobalt - 60 gamma unit (Gamma Knife).

The **Gamma Knife** contains 201 cobalt sources of gamma rays arrayed in a hemisphere within a shielded structure. A primary collimator, forces all the emitted sources to a common focal area, then a secondary collimator adapts this primary focal beam to sizes from 4 to 18 mm, through computer software, to target to the corresponding size of brain metastasis. In this case the limiting size of this device are brain metastases with a major

diameter = 18 mm or tumor volume ranged from 0.5 to 33 cm^3 (Alexander et al. 1995, Lunsford et al. 1990).
Following the same principle several authors (Betti et al. 1991, Colombo et al. 1985, Hartman et al. 1985, Giller and Berger 2005, Shoshan et al. 2005, Sperduto 2003, Valk and Dillon 1991) in the late 1980 developed **LINAC** based radiosurgical method. Linac radiosurgical treatment relies upon the following aspects: a) a collimated X-ray is directed stereotactically to the target area; b) the gentry of the linear accelerator rotates over the patient producing an arc of radiation oriented on the target. In this manner different arc or multiple non-coplanar intersecting arcs of radiation are used. Some important aspects of Linac therapeutic methodology are to be evidenced, they are: size, dose, toxicity.

3.2.1 Size of target tumor volume

Brain metastases have been considered ideal targets for radiosurgery and stereotactic radiotherapy due to their small spherical size, non-infiltrative borders, and location in non-eloquent areas of the brain. In terms of stereotactic radiosurgery, the superiority of one energy source over another depends primarily on the dose distribution capabilities, which in turn depend on the target's volume, location, and shape. For small lesions (= 5 cm^3), the dose distributions produced by the gamma knife are essentially identical to those achievable with LINAC units. When the target lesion is non -spherical or of intermediate size (=5 or = 25 cm^3), LINAC units may have an advantage over Gamma Knife units, due to their ability to treat larger lesions without requiring multiple isocenters (which makes treatment planning difficult), and the ability to shape the dose using collimated fields (Giller and Berger 2005).

3.2.2 Dose fractionation

Standard radiobiological principles suggest that fractionating radiation therapy (i.e., delivery in multiple sessions) will reduce both early and late toxicities to surrounding normal tissues. Radiotherapy can be delivered in a single session and is called radiosurgery, or in different sessions and is called: Stereotactic radiotherapy (SRT) or Conformal RadioTherapy (CRT) (Giller and Berger 2005, Shoshan et al. 2005, Sperduto 2003, Valk and Dillon 1991).

3.2.3 Toxicity (radioprotection)

Radiosurgery, notwithstanding its precision is not devoid of severe side effects on brain parenchyma, the worse being radionecrosis.CNS damage occurs in three different stages. The acute post radiation stage is usually well tolerated and consists in headache, nausea and somnolence. These symptoms are related to the cerebral edema and can be controlled with corticosteroids. A sub-acute stage caused by transient demyelization mediated damage to oligodendrocytes. This demyelization is clinically manifested by numbness, irritability, anorexia, somnolence and sometimes dysfunction of electric conduction. These symptoms occur approximately 10 weeks after cranial irradiation. Late effects (radionecrosis) become manifest from 6 to 9 months later and can evolve for a number of years following cranial irradiation. The process is associated with glia proliferation, mononuclear cell / astrocyte activation, and astrocyte secreted protein loss and cytokines production (Baker and Krochak 1989, Michalowsky 1986). The endothelium damage is the principal target of irradiation, is irreversible and progressive and determines an increase in the blood brain permeability

(Valk and Dillon 1991). The leakier endothelium determines an increment in the quantity of fluid in the interstitium, an excessive production of free radicals due to the iron loss by red blood cells and an increased production of proinflammatory prostaglandins and cytokines (see Fig.1) (Michalowsky 1986, St Clair and Given 2003, Wong and Van der Kogel 2004). An interesting study by Kureshi et al. (1994) on frozen specimen obtained by patients with radionecrosis has shown that all specimen were infiltrated with both CD4+ and CD8+ cells and activated macrophages (CD11c+, HLA-DR+). Furthermore they analyzed a panel of cytokines and found that Tumor Necrosis Factor- α (TNF-α) and Interleukin-6 immunoreactivity was prominent in majority of the specimen (75%) and were predominately produced by macrophages. TGF-[beta] astrocytic and macrophage immunoreactivity was present at moderate levels in all cases. Other authors have outlined that radiation injury is not only maintained by the inflammatory reaction elicited by radiation but is self maintained by the induction of apoptosis of endothelial cells (Wong and Van der Kogel 2004). These authors have also outlined the importance of hypoxia and VEGF production and of increased release of nitric oxide (NO) (Wong and Van der Kogel 2004). Belka et al. 2001, in agreement with us have outlined that radiation injury is the result of a complex alterations and that no single mechanism is responsible of the event. At least four factors contribute to central nervous system toxicity: (1) damage to vessel structures, (2) deletion of oligodendrocytes, (3) deletion of neural stem cells, (4) generalized alterations of cytokine expression (Kureshi et al. 1994). Actually no definitive therapies exist for radionecrosis (Valk and Dillon 1991, Belka et al 2001, Nieder et al 2007), however high dosage of corticosteroids, stem cell transplantation or erythropoietin (EPO) have been suggested. Pleiotropic functions of EPO on CNS have been recognized such as: inhibition of apoptosis, anti-inflammatory anti oxidative effects, prevention of glutamate-induced toxicity and stimulation of angiogenesis (Wong and Van der Kogel 2004). Other authors have proposed melatonin as radioprotective agent (Vijayalaxmi et al. 2004). Hyperbaric oxygen has been also proposed, however as outlined by Wong and Van der Kogel (2004), has not demonstrated a benefit. Since 1999, for brain metastases, a radioprotector formed by an association between bioflavonoids (silymarin) and omega three fatty acids has been suggested by an Italian group to decrease the risk ratio of developing brain necrosis and to improve significantly survival time (Gramaglia et al 1999). Omega 3 fatty acids have demonstrated to decrease the synthesis of proinflammatory prostaglandins (Fig.1) and cytokines, to have antitumoral activity and to change many tumor environmental parameters (Baronzio et al. 1994) whereas bioflavonoids have elicited protection of neuronal cells from oxidative stress and glutamate (Ishige et al 2001). A recent review on silymarin by Agarwaal et al. (2006) has outlined that this bioflavonoid has important anti-inflammatory and antiangiogenic activity. A vision of the various point of activity of these two natural drugs is illustrated in Fig.1.

As previous described, **Linac radiosurgery** technology delivers high doses of ionizing radiation to small intracranial targets. SRT or CFRT requires: adequate a) **patient immobilization**, b) accurate **three – dimension dose calculation TP** (treatment planning); c) **X-rays collimation**.

a. **The patient immobilization.** SRT is done using a frame fixed to patient's skull using four pins. These pins are anchored into the periosteum and afford an excellent immobilization. The method is not devoid of side effects such infections and pain. Anesthetic is used during the procedure to control this last side effect. For treatment

that last several weeks the immobilization device should be reproducible and in this case an individual customized thermoplastic mould is built.

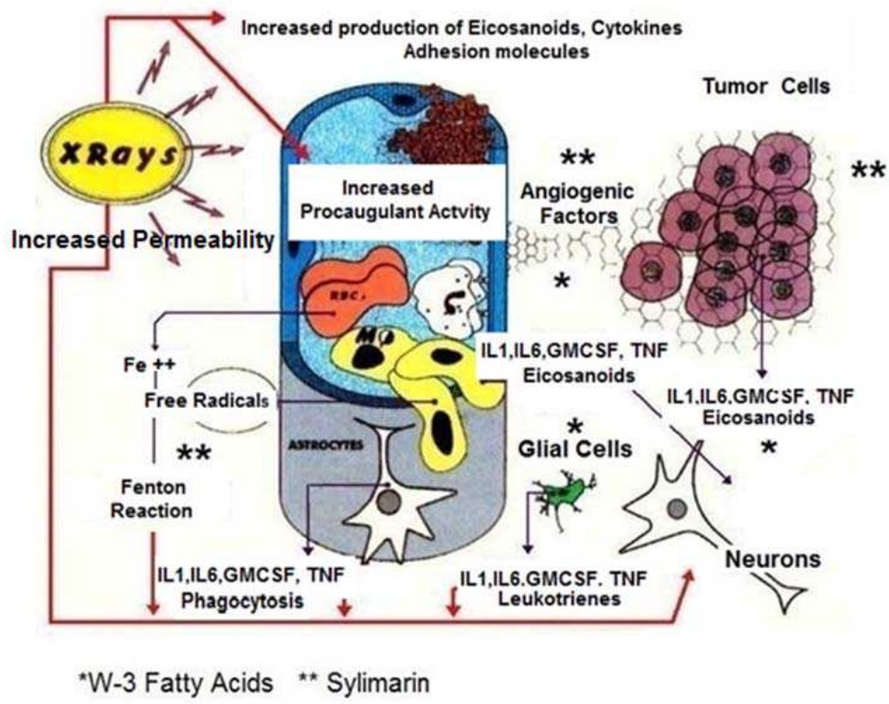


Fig. 1. In this figure, the effects of Radiotherapy on Brain structure, the reactions produced and the targets of radioprotectors such as Sylimarin ** and omega 3 fatty acids (W-3) * are illustrated.

b. **Treatment Planning.** After careful positioning the patient, is immobilized with thermoplastic moulds or with stereotactic frame undergoes to a contrast enhanced brain Computed Tomography (CT) or to a Brain Magnetic Resonance (MRI) scans with 2-5 mm slice thickness and 2-5 mm separation. Once obtained the CT/MR data, these are processed using a computerized treatment planning. CT/MRI images are fused using image fusion software and the Gross Tumor Volume (GTV) is defined and contoured manually. In some departments an integration of images with metabolic information such as Single Photon Emission Computed Tomography (SPECT) is also used (Mongioj et al 1999).This permits sometimes to obtain more accurate tumor visualization. The fusion of images is obtained by commercial software (i.e. package SRS PLATO®) consisting of three principal algorithms: (1) a module dedicated to the localization of each tomographic section on stereotactic space; (2) a CT/MR dedicated module for the creation of regions of interest (ROIs) for each slice and (3) a 3D- visualization module. Once the GTV is obtained, a margin over these countered borders must be defined to take into account the possible microscopic extension of the tumor not evidenced on the CT/MR scans. These margins are generally 10-20 mm around the GTV obtaining the Planned Target Volume (PTV). After PTV determination, a new contour is done ensuring PTV coverage by 95% isodose line with the aim for obtaining uniform dose homogeneity.

c. **Collimator.** The major problem in radiosurgery is treating irregularly shaped lesions. The use of overlapping spherical treatments results in some shaping advantages but the increased time used to reproduce this technique determines a non-homogeneous dose deposition and an increase on side effects. Improved tumor dose homogeneity can be obtained using a field shaping device able to form an optimal field shape for each beam direction (Kurup et al 2007). To obtain the best dose distribution different devices have been set up (i.e. 3D line®, Radionics ®) (Gauer et al. 2008, urie et al. 2001). Generally, these collimator devices consist of two opposing banks tungsten leaves and allows shaping of a radiation field up to a size of 11 x 10 cm^2 at the isocenter. Mechanical and dosimetric evaluations are performed to test the stability of the mechanical isocenter and to determine leaf leakage, penumbra width, and accuracy of leaf positions and uniformity of leaf speed. Several multileaf collimators are commercially available and differ from each other by many aspects such as: Leaf pairs, field size, leaf width, leaf transmission, maximum speed and total weight. As example, in table 1 we report some of the characteristics of 3D line® and that of Radionics ®.

	Radionics	3Dline
Leaf pairs	31	24
Field size(cm^2)	10x12	11x10
Leaf Width (mm)	4	4.5
Focused design	Single	Double
Total weight (Kg)	35	35
Maximum speed (cm/s)	2.5	1

Table 1. Comparison of Some Characteristics of Radionics ® and 3Dline ® multileaf Collimator

4. Current debates on the best treatment options

An important question arises: is SRT efficacious as surgery in achieving local control (Rao et al. 2007)? As reviewed by Sperduto (2003), SRT is as good as or even better than surgical resection in term of local control. Another prospective study has addressed this question (Mucacevic et al. 2006). Mucacevic et al. 2006 found that local control was superior in SRT treated patients compared to surgery, and that SRT group had a greater improvement in quality of life even if a higher rate of distant brain failure was present.

Another question is: can SRT be used only for multiple brain metastases? Previous studies suggested that use of radiosurgery for brain metastases should be limited to patients with three or fewer lesions (Gupta 2005, Andrews et al. 2004). A recent randomized trial, compared whole-brain radiation therapy (WBRT) plus radiosurgery boost to metastatic foci. This trial has demonstrated a significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure, and that the result also present among patients with 2, 3, or 4 metastases (Andrews et al. 2004). Survival also did not depend on number of metastases. The drawback of this technique is the risk of radiation necrosis. Chang et al. (2000) found that radionecrosis occurred in the 5.4% of patient treated and only 7 tumors

required subsequent surgical resection. Regarding toxicity by adding SRT + WBRT however, Aoyama et al. (2006) found no difference between the group treated with SRT alone or the group treated with SRT + WBRT. Furthermore they found that the patients in whom WBRT was omitted had a higher rate of failure in the brain (76%vs. 48%) and required salvage therapy more often for recurrent brain metastases.

Study by Hidefumi et al. 2006, has clearly evidenced that WBRT associated to SRT improve the survival of patients with 1 to 4 brain metastases. Furthermore these authors outlined that intracranial relapse occurred more frequently in patients who did not receive WBRT. A recent study however indicate that SRT boost after WBRT for single brain metastases improves survival in select patients, whereas for patients up to four metastases the association improves local control not overall survival (Eichler and Loeffler 2007). Patchell et al. (1998) and Sneed et al. (2002) however disagree and from their retrospective and prospective data suggest that omitting WBRT does not result in shorter survival. They outline that the status of systemic disease is the predominant determinant of patient's prognosis. To our opinion WBRT can omitted on selected patients with high risk of radionecrosis (increased accumulation of gadolinium in tumor area, neuro cognitive deterioration, persistence of headache and peritumoral edema) or if a close follow-up can be ensured to the patients treated with SRT. If patients do not show increased risk of radionecrosis, have a Karnofsky index > 70% and the systemic
disease is minimal WBRT is however mandatory.

4.1 Chemotherapy

As outlined by Nguyen and De Angelis 2004, chemotherapy has a limited role in treating brain metastases and is used after failure of surgery and or radiation therapy. Many chemotherapy drugs do not cross the blood-brain barrier but can reach malignant tumors in the brain, presumably through a local breakdown in the blood-brain barrier. In some chemotherapy-sensitive tumors like, lymphoma, small cell lung cancer (SCLC) and breast cancer (Eichler and Loeffler 2007), chemotherapy can induce remissions, but its routine use is still under evaluation. But for most tumors, chemotherapy for brain metastases is ineffective, may be because of the existence of the BBB. In fact, many drugs do not cross easily BBB, and do not remain in the brain long enough or at high concentration to ensure adequate cancer killing effect (Tosoni et al. 2004). Drugs active on primary tumors may not be as active on metastases (Chang et al. 2007, Cavaliere and Shiff 2007). On the contrary other authors outline that brain metastases are as responsive as primary systemic cancer. This has been demonstrated by numerous phase II studies (Tosoni et al. 2004).

Different chemotherapeutic regimens have been used for treating brain metastases from SCLC [52, 101]. Drugs have been used as single agent or combined to other drugs or associated with WBRT or SRT. The most active single drugs are cisplatinum (CCP), and temozolomide (TMZ) (Nguyen and De Angelis 2004). Cisplatinum alone has shown a response rate (RR) of 30% (Tosoni et al. 2004). A better response of 50% rate has been obtained combining to cisplatinum, etoposide, cyclophosphamide, methotrexate, and 5 fluouracil (Tosoni et al. 2004). The association with WBRT was better in term of overall survival and in treatment response (57% vs 22%) compared to patients who had received only WBRT (Postmus et al. 2000).

Breast cancer is sensitive to chemotherapy (Cavaliere and Shiff 2007). Rosner et al (1986) have shown a 50% response rate among 100 women treated with different regimens. The most common agents are: cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate, and vincristine. All these agents do not cross BBB notwithstanding a response by metastatic foci have been obtained. This outlines that BBB is not so important and that the appropriate regimen and the chemosensitivity of the metastases are more important. Boogerd et al. 1992, reported a 59% RR, and according to Rosner et al. (1986), suggest that chemotherapeutics may cross BBB at a sufficient concentration to achieve a clinical effect. Another interesting and a standard drug on breast cancer is doxorubicin. Doxorubicin does not cross easily BBB however when encapsulated in liposomes its penetration can increase (Siegal et al. 1995). Caraglia et al. (2006) used liposomal doxorubicin and temozolomide (TMZ) in 19 patients with brain metastases. This association resulted in a RR of 37%; furthermore 8 patients had complete response and 2 a partial response. Temozolamide has limited activity against breast cancer so the majority of the response may be attributed to doxorubicin (Cavaliere and Shiff 2007).

The incidence of metastases in breast cancer increases with the increase in HER2 overexpression. HER2 is an 185KDa transmembrane tyrosine kinase with extensive homology to the epidermal growth factor receptor. Trastuzumab is a monoclonal antibody (MOaBs) now approved as a first line chemotherapy in patients with positivity for HER2 receptors. After its introduction however an increased incidence in brain metastases has been noted. Retrospective studies documented an incidence between the 25% and the 40%, suggesting that HER-2 positive tumors have a biological predisposition to metastasize to brain (Lin and Winer 2007). The reasons for this increased incidence, as reported by Lin and Winer (2007), are multifactorial and include biological and treatment related factors. This last factor seems linked to the low penetration across BBB of Trastuzumab. Recently, to overcome this problem, Lapatinib has been suggested. Lapatinib has a dual inhibitor activity on epidermal growth factor and on HER2 and in preliminary has shown an objective response in two patients among 39 treated (Lin et al. 2006). Other studies with lapatinib and other HER2 inhibitors are currently been tested (Lin and Winer 2007).

The incidence of brain metastases in melanoma is high and can reach the 43%. Melanoma is relatively chemoresistant. The various biological treatments such as interferon or interleukin-2 and chemotherapeutics (dacarbazine) have shown a limited activity. Temozolomide (TMZ) has demonstrated a relatively important response against brain metastases from melanoma. TMZ is a third generation alkylating agent that can be taken orally. Its small size and lipophilic properties, allows TMZ to cross easily BBB. CNS concentrations can reach 30% of the plasma concentrations. When it has reached the CNS, TMZ is converted to the active metabolite (MTIC). TMZ has been used as a single agent or combined with WBRT (Cavaliere and Shiff 2007). For example, in a phase II study on 151 patients (Agarwala et al. 2004), , 39 patients (26%) showed a stable disease. Other authors have reported similar results, futhermore the association of TMZ with WBRT resulted in a better overall survival compared to TMZ alone (9 months versus 5 months) (Hoffman et al. 2006).

4.2 Hyperthermia and metabolic inhibitors, the future?

Multiple attempts have been made to improve the results of WBRT alone or combined with SRT/CFRT, by adding radiosensitizing agents. All the trials failed to demonstrate any

benefit either in local control or in survival (Eichler and Loeffler 2007). When brain metastases reach a critical mass > 1-2 mm^3 (10^6 cells) and a distance from host nutritive vessel > of 100-200 μm develop area of hypoxia and angiogenesis. Hypoxia results in radioresistance (Wouters et al. 2007). Actually, no definitive clinical therapies exist for overcoming tumour hypoxia out of hyperthermia (HT) (Pontiggia et al. 1990, Baronzio et al. 2006). HT is a treatment raising the temperature of tumor - loaded tissue to 40-43 degrees C. It is deprived of important side effects and has shown to enhance the effects of radiotherapy and to potentiate the efficacy of certain drugs, such as nitrosurea, cisplatinum, metothrexate (Baronzio et al. 2006, Dewey et al 1977). HT combined with radiation has been reported to yield higher complete and durable responses than radiation alone in superficial tumors. Despite difficulties in increasing human tumor temperatures, recent clinical trials have shown that a combination of hyperthermia with radiation is superior to radiation alone in controlling many human tumors (Dewey et al. 1977, Gabriele and Roca 2006). The increased effect seen by combining cytotoxic agents with hyperthermia is complex, but may be due to altered drug pharmacokinetics such as increased solubility (e.g. nitrosureas and alkylating agents), altered plasma protein binding (e.g. cisplatinum) and activation of enzymatic processes (e.g. anthracyclines) (Luk and Hulse 1980, Gerweek 1985). Hyperthermia does not usually cause marked increase in radiation side effects. Regarding brain, Seegenschmiedt et al. (1995), in their review affirmed that treatment toxicity to brain, is relatively low and long-term side effects are similar to that observed to RT alone. Ikeda et al. (1994), studied the toxicity of radiofrequency interstitial HT in dog and found alteration of Blood Brain Barrier (BBB). Other authors outlined that the maximum tolerated heat dose to CNS lies in the range of 40-60 min at 42-42.5°C or 10-30 min at 43°C (Gerweek 1985). A recent review by Sharma and Hoopes (2003) has reported that HT specifically alters the mammalian CNS. The morphological alterations for temperature in the range 40°C to 42 °C for 4 hours has been demonstrated for the axons, the glial cells and the vascular endothelium. Sneed and Stea 1995, demonstrated in a randomized study that HT has an acceptable toxicity, in fact no grade 5 toxicity was found outside 4 patients on 112 (3.5%) with grade 2 and 7 (Sneed et al. 1995).

There are only a small number of studies on brain metastases with HT. In an interesting study reported by Pontiggia on 17 patients with lung cancer,the patients were treated with nitrosurea and capacitive HT for 60'. Sixteen patients out of 17 responded with clinical improvement and radiological regression of the disease. The survival time was in median 12.7 months (Pontiggia et al. 1995).

Hyperthermia is a useful adjunct to chemotherapy and radiotherapy; however, new therapeutic strategies easily applicable in many institutions are to be developed.

The search for functional characteristics that allow cancer cells to spread to brain and development of new animal models will open new opportunities in target and drug discovery (Gril et al. 2010). Metabolic profiles of cells with metastatic propensity to brain may be one of these targets. In fact, studies by proteomics have demonstrated that breast cancer cells that metastasize to brain , have a unique protein profile consistent with increased expression of enzymes involved in glycolysis, tricarboxylic acid cycle, and oxidative phosphorylation pathways, permitting to these cells to have an enhanced proliferation and adaptation (Chen et al. 2007). Studies by Blasberg et al. (1985), using 14C-deoxyglucose and quantitative autoradiography in metastatic walker 256 brain tumors confirm that glucose utilization is of primary importance in metastatic cells and that brain

metastases consume glucose in presence of a low oxygen tension, the so called aerobic glycolysis or "Warburg effect" (Warburg 1956).
Palmieri et al. 2009 have confirmed the "Warburg effect" analyzing resected human brain metastases of breast cancer through real time PCR. They demonstrated an upregulation of hexokinase-2, an enzyme that mediates the first step of glucose metabolism, its upregulation is associated with a poor prognosis (Palmieri et al.2009). Hennipman et al. (1988) suggested an association of an increasing rate of enzymes implicated in glycolysis in breast cancer metastases and that their activities were higher in metastases compared to the primary tumors (Richardson et al. 2008). Another study on MCF10 model of mammary carcinoma by Richardson, confirms the major shift toward aerobic glycolysis (Gambhir et al. 2001). Increased glycolysis at metastatic site has been confirmed by [18F] 2-fluoro-2-deoxy-D-glucose positron emission tomography (PET) (Richardson et al. 2008, Gambhir et al. 2001, Gillies et al. 2008, and Lee et al. 2008).
Our group (Guais et al. 2010) has developed a drugs combination able to alter two different steps of tumor metabolism (pyruvate dehydrogenase and ATP citrate lyase). The first drug is α-lipoic acid (ALA), which, as is the case for dichloroacetate, inhibits the enzyme Pyruvate Dehydrogenase Kinase-1 (PDHK1). Inhibition of PDHK1 can restore the activity of pyruvate dehydrogenase, thus possibly redirecting aerobic glycolysis to respiration and thus decreasing the amount of lactate produced. The second drug is hydroxycitrate (HCA), which inhibits ATP citrate lyase. The efficacy of this combination appears in animals to be similar to conventional chemotherapy (cisplatin or 5-FU), as it results in both significant tumor growth inhibition and enhanced survival (Schwartz et al. 2010). Similar results have been obtained in one case of pancreatic patient metastatic to liver (Guais et al. 2010). An unpublished result, of a patient with head and neck cancer with brain metastases treated with ALA and HCA and chemotherapy has shown a complete disappearance of brain metastases (personal communication).
Immunohistochemistry studies on several specimens of primitive and metastatic human cancers, such as colon, breast, lung, ovarian and pancreas, have, also revealed an overexpression of hypoxia- inducible factor 1 (HIF) (Zhong et al. 1999). This overexpression supports two basic biological behavior of cancer and its metastases, an altered glucose transport and a limited diffusion of O_2, glucose and nutrients (Liu et al. 2002). Hypoxic tumor cells become hypersensitized to glycolytic inhibitors (Liu et al. 2002) and to hyperthermia (Baronzio et al. 2006), reinforcing our hypotheses on metabolic treatment of metastatic cancer.

5. Discussion and conclusions

Patients with brain metastases have usually a short survival. Historical studies have demonstrated that with no treatments the survival is of the order of one - two months, due to systemic progression in sites other than brain. Although brain metastases incidence is increasing, there is no consensus for their treatment. Currently, treatment options include WBRT, surgery, chemotherapy and SRT/CRT. WBRT has the advantage of being easily and widely available and is able to extend survival to three to six months. In the case of solitary metastases, the addition of surgical resection to WBRT has doubled the survival, in the range of 10 - 12 months (Patchell et al. 1990, Heilbrun and Adler 2010). However, many patients have metastases in locations not amenable to surgical resection. STRT, for these patients has demonstrated in terms of survival and palliation to be a reliable clinical tool

(Brown and Pollock 2005). For larger lesions surgery could be considered when feasible in alternative to STRT even though in our opinion the SRT as first attempt could avoid the risk of seeding and partial resection. Surgery, in our institution, showed its major role in two different settings, i.e. for solitary brain disease with a controlled disease outside the brain and for resection of large necrotic masses, as result of previous STRT (mainly for lesions of more than 45 mm of diameter). A recent work has confirmed that previous surgical treatments have a negative impact on survival, suggesting that intervention must follows SRT (Vijayalaxmi et al 2004). As outlined by De Angelis (1994), another biological aspect, favoring the use SRT compared to WBRT, relies on that, approximately half of patients have single metastases and 20% of patients have only two metastatic lesions at the moment of their diagnosis. This aspect suggests that metastases to brain must be considered and treated as a local disease process. We suggest that the correct approach to patients bearing brain metastases should have to consider palliation as first intent. SRT, which reach this need faster than WBRT, is to be considered the treatment of choice mainly for patients bearing up to 3 lesions at first diagnosis, reserving WBRT as adjuvant to SRT and for palliation attempt to those with more than 3 lesions. Surgery must be used for patients without evident primary tumor and for necrotic lesions following aggressive radiotherapy. Furthermore, the altered glucose metabolism of metastases, suggests that the metabolic treatment is a promising line of research that could have significant therapeutic applications in a near future.

6. References

Agarwal R, Agarwal C, Ichikawa H et al: Anticancer potential of silymarin: from bench to bed side. Anticancer Res. 2006; 26:4457-98.

Agarwala SS, Kirkwood JM, Gore M, et al: Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol. 2004; 22 :2101-2107.

American College of Surgical oncology CNS Working Group: The management of brain Metastases. In Principles of Neuroncology. David Schiff and Brian Patrick O'Neill Editors. pp553-579, 2005 McGraw- Hill, New York, London, Toronto.

Alexander EIII, Moriarty T.M., Davis R.B., et al: Stereotactic Radiosurgery for the definitive, non invasive treatment of brain metastasis. J Natl Cancer Inst 1955; 37: 34-40.

Andrews D.W., Scott C.B., Sperduto P.W., et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial: The Lancet 2004, 363:1665-1672.

Aoyama H, Shirato H, Tago M, et al: Stereotactic radiosurgery plus whole brain radiotherapy vs. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295: 2483-2491.

Baker AB: Metastatic tumors to the nervous system. Arch Pathol 1942;24: 495-537.

Baker D.G. and Krochak R.J.: The response of microvascular system to radiation. A review. Cancer Investigation 1989;7: 287-294.

Baronzio G:F.,Freitas i, Griffini P; et al: Omega-3 fatty acids can improve radioresponse modifying tumor interstitial pressure, blood rheology and membrane peroxidability. Anticancer res 1994,14.1145-1154.

Baronzio G.F., Cerreta V, Baronzio A;, et al: Thermo chemo-radiotherapy association: Biological rationale, Preliminary observations on its use on Malignant brain tumors. "Hyperthermia in Cancer treatment: A primer" Baronzio G.F. and Hager D editors, Landes / Springer 2006, pp:123-151.

Belka C, Budach W, Kortmann R.D. et al: Radiation induced CNS toxicity-molecular and cellular mechanisms. British J Cancer 2001,85:1233-1239.

Beasley KD, Toms SA. The molecular pathobiology of metastasis to the brain: a review. Neurosurg Clin N Am. 2011 Jan;22(1):7-14.

Betti O.O., Galmarini D, Derechinsky V. radiosurgery with a linear accelerator. Methodologic Aspects. Stereotac Func Neurosurg 1991;57.87-98.

Bindal R.K., Sawaya R, Leavens M.E., et al: Surgical treatment of multiple brain metastases. J Neurosurg 1993;79:210-216.

Blasberg RG, Shinohara M, Shapiro WR, Patlak CS, Pettigrew KD, Fenstermacher JD.Apparent glucose utilization in Walker 256 metastatic brain tumors. J Neurooncol. 1985;3(2):153-64.

Boogerd W, Dalesio O, Bais E.M. et al: response of brain metastases from breast cancer to systemic chemotherapy. Cancer 1992; 69: 972-980.

Brown P.D. and Pollock B.E. Principles of Radiotherapy and Radiosurgery In Principles of Neuroncology. David Schiff and Brian Patrick O'Neill Editors . pp553-579, 2005 McGraw- Hill, New York, London, Toronto.

Bucana CD, Yano S, Reynolds D, Fidler IJ.: 22 morphometric investigation of immunostained blood vessels in brain metastasis in nude mice.J Histochem Cytochem. 1999 ; 47:1647C-1648.

Buchsbaum J.C., Suh J.H., Lee S.Y., et al: Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 2002;94: 2265-2272.

Caraglia M, Addeo R, Costanzo R et al: Phase II study of temozolamide plus pegylated liposomal doxorubicin in the treatment of brain metastases from solid tumors. Cancer Chemother Pharmacol. 2006; 57: 34-39

Cavaliere R and Schiff D: Chemotherapy and cerebral metastases: Misperception or reality? Neurosurg Focus 2007, 22 : 1.9.

Chang S.D., Lee E, Gordon R.N.;et al: Stereotactic radiosurgery in patients with multiple brain metastases. Neurosurg Focus 2000; 9: 1-5.

Chang J.E., Robins H.I., Mehta M.P.: Therapeutic advances in the treatment of brain metastases. Clinical advances in Hematology & Oncology. 2007; 5: 54-64.

Chason JL, Walker FB, Landers JW: Metastatic carcinoma in the central nervous system and dorsal root ganglia. A prospective autopsy studied. Cancer 1963;16:781-787.

Chen E, Hewell J, Krueger J, et al: Adaptation of energy metabolism in breast cancer brain metastases. Cancer Res. 67: 1472-1486.

Chenyu Zhang and Dihua Yu : Microenvironment Determinants of Brain Metastasis. Cell & Bioscience 2011, 1:8 .

Colombo F, Benedetti A, Pozza F., et al: Stereotactic radiosurgery utilizing a linear accelerator. Appl Neurophysiol 1985;48:133-145

Cormio G, Maneo A, Colamaria A, et al. : Surgical resection of solitary brain metastasis from ovarian carcinoma: an analysis of 22 cases. Gynecol Oncol. 2003;89: 116-119.

D'Ambrosio A, Agazzi S: Prognosis in patients presenting with brain metastases from an undiagnosed primary tumor. Neurosurg Focus. 2007;22:1-7.

Delattre JY, Krol G, Thaler HT, et al.: Distribution of brain metastases. Arch Neurol. 1988;45:741-744.

DeAngelis LM. Management of brain metastases. Cancer Invest. 1994;12(2):156-65.

Deeken J-F- and Löscher W: The blood brain barrier and cancer: transporters, treatment, and Trojan horses. Clin Cancer Res. 2007,13.1663-1674.

Deichman GI: Natural host resistance and in vivo selection of malignant tumour cells. Cancer Surveys 1998. 7:675-690.

Denkins Y, Reiland J, Roy M et al. Brain metastases in melanoma: roles of neurotrophins. Neuro-Oncology 2004;6:154-165

Dewey WC, Hopwood LE Sapareto SA et al. :Cellular responses to combinations of hyperthermia and radiation. Radiology 1977;123: 463-474.

Dong J.T., Lamb P.W., Rinker-Schaeffer C.W., et al: KA11, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. Science 1995, 268.884-886.

Eichler A. F., Loeffler J. S.: Multidisciplinary management of brain metastases. The Oncologist 2007;12: 884-898.

Fidler IJ, Schackert G, Zhang RD, Radinsky R, Fujimaki T. The biology of melanoma brain metastasis. Cancer Metastasis Rev. 1999;18(3):387-400.

Fidler IJ, Yano S, Zhang RD,ety al: The seed and soil hypothesis: vascularisation and brain metastases. Lancet Oncol. 2002;3:53-7.

Fidler IJ. Critical determinants of metastasis. Semin Cancer Biol. 2002; 12:89-96. Gupta G.P.and Massagué J: Cancer metastasis: Building a framework. Cell.2006;17: 679-695.

Fidler IJ, Kim S-J and Langley R.R.: The role of the organ environment in the biology and therapy of cancer metastasis. J. Cell. Biochem. 2007;101:927-936.

Fidler IJ, Balasubramanian K, Lin Q, Kim SW, Kim SJ. The brain microenvironment and cancer metastasis. Mol Cells. 2010 Aug;30(2):93-8.

Gabriele P and Roca C:Results of hyperthermia alone with radiation therapy and or / chemotherapy. In "Hyperthermia in Cancer treatment: A primer" BAronzio G.F. and Hager D editors, Landes/Springer 2006, pp:114-119.

Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME.: A tabulated summary of the FDG PET literature. J Nucl Med. 2001 May;42(5 Suppl):1S-93S.

Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials.Int J Radiat Onc ol Biol Phys. 1997 ;37(4):745-51.

Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys. 2000;47:1001-6.

Gauer T, Sokoll J, Cremers F, Harmansa R, Luzzara M, Schmidt R.Characterization of an add-on multileaf collimator for electron beam therapy.Phys Med Biol. 2008 Feb 21;53(4):1071-85.

Gerweck L. E.: Hyperthermia in Cancer Therapy: The Biological Basis and Unresolved Questions[1] *Cancer Research* 1985, 45, 3408-3414.

Gillies RJ, Robey I, Gatenby RA. : Causes and consequences of increased glucose metabolism of cancers. J Nucl Med. 2008 Jun;49 Suppl 2:24S-42S.

Giller C.A., and Berger B.D.: New frontiers in radiosurgery for the brain and body. BUMC Proceedings. 2005; 18:311-319.

Globus JH, Meltzer T. Metastatic tumors of the brain. Arch Neurol Psychiatr. 1942;482:163-226.

Gramaglia A, Loi G.F., Mongioj V, and Baronzio G.F.: Increased survival in brain metastatic patients treated with stereotactic radiotherapy, omega three fatty acids and bioflavonoids. Anticancer res 1999; 19. 5583-5586.

Gril B, Evans L, Palmieri D, Steeg PS.: Translational research in brain metastasis is identifying molecular pathways that may lead to the development of new therapeutic strategies. Eur J Cancer. 2010 May;46(7):1204-10.

Guais A, Baronzio G, Sanders E, Campion F, Mainini C, Fiorentini G, Montagnani F, Behzadi M, Schwartz L, Abolhassani M.: Adding a combination of hydroxycitrate and lipoic acid (METABLOC™) to chemotherapy improves effectiveness against tumor development: experimental results and case report. Invest New Drugs. 2010 Oct 8.

Gupta T: Stereotactic radiosurgery for brain oligometastases: good for some, better for all. Annals of oncology 2005; 16:1749-54.

Hammoud M.A., McCutcheon I.E:, Elsouki R, et al: Colorectal carcinoma and brain metastasis: distribution, treatment, survival. Ann Surg Oncol 1996; 3: 453-463.

Hankins J.R., Miller J.E., Salcman M, et al: Surgical management of lung cancer with solitary cerebral metastasis. Ann. Thorac. Surg. 1988;46:24-28.

Hartmann G.H., Schlegel W, Strum V,et al: Cerebral radiation surgery using moving field irradiation at a linear accelerator facility. Int J Radiat Oncol Biol Phys.1985,11.1185-1192.

Heilbrun MP, Adler JR. The 2009 devaluation of radiosurgery and its impact on the neurosurgery-radiation oncology partnership. J Neurosurg.2010,Jul;113(1):10-5.

Hennipman A, van Oirschot BA, Smits J, Rijksen G, Staal GE. : Glycolytic enzyme activities in breast cancer metastases. Tumour Biol. 1988;9(5):241-8.

Hidefumi A, Hiroki, Masao T, et al: Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases *JAMA*. 2006;296:2089-2090.

Hofmann M, Kiecker F, Wurm R et al: Temozolomide with or without radiotherapy in melanoma with unresectable brain metastases. IJ Neurooncol 2006; 76: 59-64.

Hwang TL, Close TP, Grego JM et al: Predilection of brain metastases in gray and white matter junction and vascular border zones. Cancer 1996;77:1551-11555.

Ikeda N, Hayashida O, Kameda H et al: Experimental study on thermal damage to dog normal brain. Int. J. Hyperthermia. 1994;10:553-561.

Ishige K, Shubert D, Sagara Y: Flavonoids protect neuronal cells from oxidative stress by three distinct mechanisms. Free radical Biology & Medecine 2001;30: 433-446.

Iwadate Y, Namba H, Yamaura A: Significance of surgical resection for the treatment of multiple brain metastases. Anticancer Res 2000;20: 573-577.

Kamar FG, Posner JB. Brain metastases. Semin Neurol. 2010 Jul;30(3):217-35.

Kang M, Fujimaki T, Yano S and Fidler I: Biollogy of brain metastasis from: Contemporary cancer Research: Brain Tumors, 2004: pp 91-106, Edited by Ali-Osman F Humana Press Inc., Totowa ,NJ.

Kaplan R.N., Rafti S, Lyden D: preparing the soil: the premetastatic niche. Cancer Res. 2006; 66:11089-11093.

Kaplan R.N., Riba R.D., Zachaurolis S, et al: VEGFR1-positive haemopoietic progenitor cells initiate the premetastatic niche. Nature 2005; 438:820-827.

Kehrli P.: Biologie des métastases cérébrales. Neurochirurgie. 1999,45:364-368.

Kim LS, Huang S, Lu W et al: Vascular endothelial growth factor expression promotes the growth of breast cancer brain metastasis in nude mice. Clin Exp Metastasis. 2004,21:107-118.

Kleisbauer J.P:, Guerin J.C., Arnaud A et al: Chemotherapy with high dose cisplatin in brain metastases of lung cancer.Bull Cancer 1990;77:661-665.

Kureshi S. A.; Hofma, F; Schneider J. H.; et al: Cytokines and delayed radiation necrosis. Neurosurgery. 1994; 35:822-830.

Kurup P.G.G., Murali V, Sankar A.: Advantages of minimultileaf in stereotactic radiotherapy. Journal of Medical Physics 2007;32: 12-17.

Leone A, Flatow U, King C.R., et al: Reduced tumor incidence , metastatic potential, and cytokine responsiveness on nm23-transfected melanoma cells. Cell 1991;65:25-35.

Lin N.U., Carey L.A., Liu M.C. et al: Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancxer. J Clin Oncol 2006;3s.

Lin N.U:,and Winer E.P:: Brain metastases: The HER2 paradigm. Clin Cancer Res 2007; 13: 1648-1655.

Liu H, Savaraj N, Priebe W, Lampidis TJ. Hypoxia increases tumor cellsensitivity to glycolytic inhibitors: a strategy for solid tumor therapy (ModelC). Biochem Pharmacol. 2002 Dec 15;64(12):1745-51.

Luk K.H. and Hulse R. M. : Hyperthermia in Cancer Therapy. West J Med. 1980; 132: 179–185.

Lunsford L.D., Flickinger J, Coffey R.J.: Stereotactic gamma knife radiosurgery. Initial North American experience in 207 patients. Arch Neurol 1990;47:797-803.

Marchetti D, Denkins Y, Reiland J et al: Brain-metastatic melanoma. A neurotrophic perspective. Pathology oncology Research 2003:3: 147-158.

Menter d.G., Hermann J.L., Marchetti D et al: Involvement of neurotrophins and growth factors in brain metastasis formation. Invasion Metastasis 1994-1995;14:372-384.

Meert A.P., Paesmans M, Berghmans T, et al: Prophylactic cranial irradiation in small cell lung: a systematic review of the literature with meta-analysis. BMC Cancer 2001;1:5

McCutcheon I.E., Eng D.Y., Logothetis C.J. : Brain metastasis from prostate carcinoma: ante mortem recognition and outcome after treatment. Cancer 1999; 86:2301-2311.

Michalowsky A: the pathogenesis of late side-effects of radiotherapy. Clinical radiology 1986;37:203-207.

Mongioj V, Brusa A, Loi G.F. et al: Accuracy evaluation of fusion of CT, MR, and SPECT images using commercially available software packages (SRS Plato and IFS). Int, J. Radiation Oncology, Biol. Phys. 1999;43: 227-234.

Muacevic A, Wowra B, Kreth F, et al.: a randomized trial of surgery and radiotherapy versus radiosurgery alone in the treatment of single metastasis to the brain. Doc OP256, Deutscher Krebscongress. Berlin, Deutscher Krebscongress, 2006.

Nash G.F:, Turner L.F., Scully M.F. et al: Platelets and cancer. Lancet Oncol. 2002, 3:425-430.

Nathoo N, Chahlavi A, Barnett GH, et al: Pathobiology of brain metastases. J Clin Pathol. 2005; 56:237-242.

Nicolson G: paracrine and autocrine growth mechanisms in tumor metastasis to specific sites with particular emphasis on brain and lung metastasis. Cancer Metastasis Rev 1993.12: 325-343.

Nieder C, Andratschke N and Asner S.T:: Experimental concepts for toxicity prevention and tissue restoration after cental nervous system irradiation. Radiation Oncology. 2007,2:23-33.

Norden AD, Wen PY, Kesan S: Brain metastases. Current Opinion In Neurology.2005; 18:654-661.

Ngguyen T and DeAngelis L.M.: Treatment of brain metastases. The Journal of Supportive Oncology. 2004; 2: 405-416.

Nussbaum ES, Djalilian HR, Cho KH et al: Brain metastases. Histology, multiplicity, surgery and survival. Cancer 1996;78:1781-1788.

Palmieri D, chambers BF, Huang S et al: The biology of the metastasis to a sanctuary site. Clin Cancer Res. 2007;13: 16561662.

Palmieri D, Fitzgerald D, Shreeve SM, Hua E, Bronder JL, Weil RJ, Davis S, Stark AM, Merino MJ, Kurek R, Mehdorn HM, Davis G, Steinberg SM, Meltzer PS, Aldape K, Steeg PS.: Analyses of resected human brain metastases of breast cancer reveal the association between up-regulation of hexokinase 2 and poor prognosis. Mol Cancer Res. 2009 Sep;7(9):1438-45.

Patchell R.A., Tibbs P.A., walsh J.W:, et al. : A randomized trial of surgery in the treatment of single metastases to the brain. N. Engl J Med. 1990;322:494-500.

Patchell R.A., Tibbs P.A., Regine W.F.; et al: postoperative radiotherapy in the treatment of single metastases to the brain. A randomized trial. JAMA 1998,280.1485-1489

Patchell R A: The management of brain metastases. Cancer Treat Rev. 2003 ;29: 533-40.

Pectasides D, Pectasides M, Economopoulos T : Brain metastases from epithelial ovarian cancer:A review of the literature. The Oncologist2006;11:252-260

Perides G, Zhuge Y, Lin T et al: the fibrinolytic system facilitates tumor cell migration across the blood-brain barrier in experimental melanoma brain metastasis. BMC Cancer 2006, 6: 56-65.

Pontiggia P, McLaren JR, Baronzio GF, Freitas I: The biological responses to heat. Adv Exp Med Biol. 1990;267:271-91.

Pontiggia P, Cuppone Curto F, Rotella G, et al : Hyperthermia in the treatment of brain metastases from lung cancer. Experience on 17 cases. Anticancer Res. 1995; 15: 597-601.

Postmus P.E., Haaxama –Reiche H, Smit E.F. et al: Treatment of brain metastases of small cell lung cancer: comparing teniposide and teniposide with whole brain radiotherapy-a phase III study of European Organization for the research and treatment of Cancer Lung Cancer cooperative group. J. Clin. Oncol. 2000,18: 3400-3408.

Posner JB, Chernic NL: intracranial metastases from systemic cancer. Adv Neurol 1978; 19: 589-592

Rao R, Brown P, Buckner JC: Innovation in management of brain metastases. Oncology 2007; 21:473-481.

Richardson AD, Yang C, Osterman A, Smith JW. Central carbon metabolism in the progression of mammary carcinoma. Breast Cancer Res Treat. 2008

Rosner D, Nemoto T, Warren W.L.: Chemotherapy induces regression of brain metastases in breast carcinomas. Cancer 1986;58: 832-839.

Santarelli J.G., Sarkissaian V, Hou L et al: Molecular events of brain metastasis. Neurosurg Focus 2007; 22: E1-E5.

Seegenschmiedt MH, Feldmann HJ, Wust P et al: Hyperthermia- Its actual role in Radiation Oncology, part IV Thermoradiotherapy for malignant brain tumors. Strhlentherapie und Onkologie 1995;171:560-572.

Seraj M.J., Samant R.S., Verderame M.F., et al: Functional evidence for a novel human breast carcinoma metastasis suppressor,BRMS1, encoded at chromosome 11q13. Cancer Res 2000;60:2764-2769.

Shaffrey M.E., Mut M., Asher A.L., et al: Brain metastases Curr Probl Surg 2004;41:665-741

Sharma HS and Hoopes PJ: Hyperthermia induced pathophysiology of the central nervous system. Int. J Hyperthermia. 2003;19:325-354.

Shoshan Y.,Wygoda M and Umansky F.: Stereotactic radiosurgery and fractionated stereotactic radiotherapy: background, definition, applications. IMAJ 2005;7: 597-599.

Siegal T, Horowitz A, Gabizon A: Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: biodistribution and Therapeutic efficacy. J Neurosurg. 1995; 83: 1029-1037.

Sminia P, Van Der Zee J, Wondergem J et al: Effect of hyperthermia on central nervous system: a review. Int. J. Hyperthermia 1994;10: 1-30.

Sneed PK and Stea B: Thermoradiotherapy for brain tumors. Appeared in "Thermoradiotherapy and Thermochemotherapy" MH Seegenschmiedt , P. Fessenden and C.C. Vernon editors. Springer Verlag, Berlin, Heidelberg,New York 1995; pp 159-175.

Sneed P.K., Suh J.H., Goetch S.J, et al: a multi-institutional review of radiosurgery alone vs. Radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat. Oncol. Biol. Phys. 2002,53.519-526.

Sperduto P.W.: A review of stereotactic radiosurgery in the management of brain metastases. Technology in Cancer Research treatment 2003;2: 105-109Weil R.J, Palmieri D.C., Bronder J.L.et al: Breast cancer metastasis to the central nervous system. Am J Pathol 2005,16: 913-920.

St. Clair W.H:, Given C.A.: Stereotactic Radiosurgery associated neurotoxicity. Technology in Cancer Research treatment 2003;2: 147-151.

Schwartz L, Abolhassani M, Guais A, Sanders E, Steyaert JM, Campion F, Israël M.: A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: preliminary results. Oncol Rep. 2010 May;23(5):1407-16.

Shaffrey ME, Mut M, Asher AL, Burri SH, Chahlavi A, et al: Brain metastases. Curr. Probl. Surgery.2004;4:665-741.

Tajran D, Berek J.S.: Surgical resection of solitary brain metastasis from cervical cancer Int J Gynecol cancer. 2003;13:368-370.

Tikhtman AJ, Patchell RA: Brain metastases. In: Morantz RA, Walsh JW, editors. Brain tumors: Marcel Dekker, Inc 1995;553-556.

Tom MI: Metastatic tumors of the brain. Can Med Assoc J. 1946;54.265-268.

Tong-xin Xie, feng-ju H., Aldape K.D:, et al: Activation of Stat3 in human melanoma promotes brain metastases. Cancer Res 2006; 66: 3188- 3196

Tosoni A, Ermani M, Brandes A.A:. The pathogenesis and treatment of brain metastases: a comphrensive review. Critical reviews in Oncology /Hematology. 2004; 52:199-215.

Urie MM, Lo YC, Litofsky S, FitzGerald TJ. Miniature multileaf collimator as an alternative to traditional circular collimators for stereotactic radiosurgery and stereotactic radiotherapy. Stereotact Funct Neurosurg. 2001;76(1):47-62.

Valk P..E. and Dillon W.P.: Radiation injury of the brain. AJR 1991,156: 689-706.

Vecht C.J., Haaxma-Reich H, Noordjik E. et al: Treatment of single brain metastases: radiotherapy alone or combined with neurosurgery. Ann Neurol 1993; 33: 583-590.

Vijayalaxmi, Reiter R.J., Dun-Xian T.; et al: Melatonin as a radioprotective agent: a review. Int. J. Radiation oncology Biol. Phys. 2004, 59: 639-653.

Warburg O.: On the origin of cancer cells. Science. 1956 Feb 24;123(3191):309-14.

Wong CS, Van der Kogel AJ.: Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. Mol Interv. 2004 Oct;4(5):273-284.

Wouters A, Pauwels B, Lardon F, et al: Review: Implications of In Vitro Research on the Effect of Radiotherapy and Chemotherapy Under Hypoxic Conditions The Oncologist 2007; 12: 690-7129

Wronski M,Arbit E, Burt M, et al: Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. J Neurosurg 1995;83: 605-616.

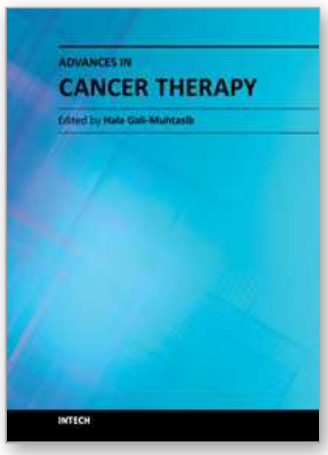
Yano S, Shinoara H, Herbst RS et al: Expression of vascular endothelial growth factor is necessary but not sufficient for production and growth of brain metastasis. Cancer Res 2000; 60.4959-4967.

Zimm S, Wampler GL, Stablein D, et al: Intracerebral metastases in solid tumor patients, natural history and result of treatment. Cancer. 1981; 48:384-394.

Zhong H, De Marzo AM, Laughner E, Lim M, Hilton DA, Zagzag D, Buechler P,Isaacs WB, Semenza GL, Simons JW. Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. Cancer Res. 1999 Nov 15;59(22):5830-5.

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