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# DETERMINANT FACTORS OF MOOD DISORDERS IN BRAIN CANCER PATIENTS: DEVELOPMENT OF NOVEL INTRAOPERATIVE TOOLS IMPACT ON PROGNOSIS AND QUALITY OF LIFE

**PhD Thesis of**

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# *SUMMARY*

# *ABBREVIATIONS LIST*

| | |
|---|---|
| AED | Antiepileptic drugs |
| AIRTUM | Associazione Italiana Registro Tumori |
| BMt | Brain Mapping techinique |
| BOLD | Blood oxygenation |
| BT | Brain tumors |
| CBTRUS | Central Brain Tumour Registry of United States |
| CD | Cognitive disfunctions/deficits |
| CG | Control Group |
| CNS | Central nervous system |
| CHT | Chemotherapy |
| CT | Computed Scan |
| DES | Direct Electrical Stimulation |
| DTI | Diffusion Tensor Imaging |
| EFs | Executive functions |
| EOR | Extend of resection |
| fMRI | Functional Magnetic Resonance |
| HF | High Frequency |
| HGG | High grade glioma |
| HRQoL | Health Related Quality of Life |
| IFG | Inferior Frontal Gyrus |
| iST | Intraoperative Stroop Test |
| iVT | Intraoperative Visual test |
| LF | Low Frequency |
| LGG | Low grade glioma |
| MD | Mood Disorders |
| MFG | Medial Frontal Gyrus |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Topografy |
| PCV | Procarbazine, Lomustine and Vincristine |
| PFS | Progression-free survival |
| QoL | Quality of life |
| RT | Radiotherapy |
| SD | Standard Deviation |
| SFG | Superior Frontal Gyrus |
| TMT | Trail Making Test |
| TMZ | Temozolamide |
| TOJ | Temporo occipital junction |
| vPM | Ventral Pre-Motor |
| VG | Visual Group |
| WHO | World Health Organization |
| WM | White Matter |

# *SUMMARY*

Brain tumour is an infiltrating disease harbouring within the central nervous system (CNS) causing Cognitive and Mood Disorders. The prognosis is very poor. The optimization of the surgical procedure with the aid of Brain Mapping Technique (BMt) allows to extending the resection of the tumour beyond its boundaries (supramarginal resection), increasing the patients' survival while preserving the patients' functional integrity, assuring them the best possible Health Related Quality of Life (HRQoL). However, despite the advanced surgical procedure, patients face many stressors in the course of the disease, among which the Cognitive deficits leading in Mood Disorders. Notably, Mood disorders, in turn, dramatically affect the HRQoL, the survival and other crucial aspect of care including the compliance to treatment (Litofsky et al. 2004, Maino et al. 2006). The negative influence of Cognitive and Mood Disorders on HRQoL is still a matter of debate. At present is indeed still unsolved the critical issue of whether are the clinical features related to the tumour, or rather the psychological response to the stressors secondary to the care, to be considered the main predicting factors for emergence of Mood Disorders in brain tumour patients (Madhusoodanan 2015).

Based on these premises the present PhD study investigated the association between Mood Disorders, the specific clinical and anatomical features related to the tumour itself, and the patients' cognitive outcome with the aim of disclosing the influence of Cognitive and Mood Disorders on HRQoL before and after treatments in patients with brain tumour and, accordingly, of developing specific "interventions" aimed at improving the patient's HRQoL.

The results of the study, conducted on 116 patients who underwent awake procedure for tumour resection, showed that Mood Disorders were not associated with the clinical features of brain tumour *per se*, as might be expected, but rather they were associated with the lack of recovery from Cognitive post-surgical deficits and, among the possible Cognitive deficits, specifically language, attentive/executive and visual deficits. Moreover the HRQoL turned out to be negatively affected by both the lack of cognitive recovery and by the occurrence of Mood Disorders, especially in the long run (3, 6 months after treatments).

Based on these results, in order to reduce the incidence of Mood Disorders and to improve the HRQoL of the patients affected by brain tumour, two new intraoperative tools designed to map and

preserve the networks involved in the attentive/executive and visual functions were designed and tested in the intraoperative setting.

The feasibility of the new "intraoperative Stroop tools - iST" and its accuracy in preserving attentive/executive functions (EF) was assessed in 45 patients affected by glioma and candidate for tumour resection during the awake-asleep-awake surgery. The results showed that iST was successfully administered intraoperatively in all patients with high feasibility and reduced dramatically the prevalence of acute and long-term post-operative EFs deficits.

The feasibility a new intraoperative Visual tool (iVT) designed to preserve visual abilities patients affected by glioma involving visual pathways was assessed in 25 patients candidate for surgical resection in awake surgery. The results showed that the iVT was successfully administered intraoperatively in all patients with high feasibility. The analysis of peripheral visual assessment showed that 17 of 25 (68%) patients did not show any post-operative visual deficits.

Conclusively the novel evidence provided by this PhD Study was that is not the Cognitive deficit induced by the treatment *per se*, but rather the patients' expectation about their recovery after treatment and their disappointment, that play a crucial role in determine the emergence of Mood Disorders, consequently negatively affecting their HRQoL. These results first highlight the importance of a proper communication of predicted deficits by the medical team. Moreover, the feasibility of a more accurate BMt implemented with new intraoperative tools (iST and iVT) and allowed to optimize the resection without affecting patient's functional integrity.

Overall this research suggests that the efficacy of a neurooncological treatment should account for both the neuropsychological outcome of treatments and also patients' expectation, delivering them realistic information and thus expectations, about their post-treatment outcome and implementing new techniques to reduce the occurrence of deficits significantly affecting the QoL of patients.

# *GENERAL INTRODUCTION*

Primary Brain Tumour (BT) is an infiltrating chronic disease of the central nervous system (CNS). In Italy, in 2010, CNS tumours affected about 27,000 persons. Considering all the CNS tumours, the survival at one year is 55% and at 5 years only 21% (AIRTUM, 2016). Within all glial tumours ependymal tumours had the best 5-year prognosis (74% overall, 80% low grade and 37% high grade). Considering the poor prognosis of this disease, most of the research conducted in centers specialized in treatment of brain tumour, focused only on patients' survival, neglecting, for a long time, others important aspects affecting life of patients, such as the well-being and quality of life of the "survivors". In fact, the treatments of brain tumour (surgery and adjuvant treatments) frequently induce motor and cognitive disorders associated with mood disorders (MD), and specifically depression and anxiety, dramatically affecting the quality of life of patients and of their families. The association between MD and the diagnosis of cancer might seem obvious, however patients with brain tumour show higher incidence of cognitive dysfunctions and MD respect to the patients with other tumours not affecting CNS (Klein et al. 2003; Janda et al. 2006; Goebel et al. 2011). In this regard, the available literature on brain tumour treatments, reports the prevalence of preoperative and postoperative psychological symptoms ranging from 5% to 89% in different studies (Litofsky et al. 2004; Maino et al. 2011). Despite the variability of these data precluding any conclusion on this issue, the significant higher incidence of MD in patients affected by brain tumour with respect to patients affected by cancer not related to CNS might suggest that the MD in brain tumour patients cannot be interpreted as the sole psychological reaction to cancer itself, but may be significantly related to some additional biological factors specifically related to this disease, although at present, in the literature there are conflicting results about the association between MD and clinical variables, including tumour location, histology, and extent of surgical resection.

Importantly, MD in brain tumour patients must not be neglected or considered of less importance with respect to the primary treatment in that, on one side they may influence, negatively, crucial aspects of care such as the compliance of treatments and eventually the survival and, on the other side, they cause a decline in functional independence more often than physical disability, with a significant impact on Health Related Quality of Life (HRQoL). Recent evidence suggests that brain tumour patients with depression or psychological symptoms show worse HRQoL, elevated risk of suicide, more clinical complications and worse survival (Pellettier et al.

2002; Litofsky et al. 2004). Coherently, improved HRQoL is associated with longer survival especially of high-grade glioma patients, while MD and poor HRQoL are associated with shorter expectance of life (Litofsky et al. 2004, Mainio et al. 2006).

The survival with a diagnosis of brain tumour depends on different indicators such as grade and molecular features, symptoms, tumour location and extent of tumour residual but also psychological disorders and patient's HRQoL. At present, the extent of resection (EOR) is reported as the main factor significantly affecting the natural history of the disease and, ultimately, the prognosis. In order to perform an extensive surgical resection of the tumour preserving the patient's functionality, it is necessary to optimizine modern surgical procedures, by implementing the tools allowing the bets resection. One of the most important technique used to perform resection of brain tumours is the brain mapping technique (BMt), that, by means of electrical stimulation, allows to performing "supra-total resections" (i.e. an extended removal of the tumour's borders beyond the MRI-defined abnormalities) while preserving the brain structures essentials for the main neural and cognitive functions. This double goal is aimed at increasing the patients' survival or free progression survival and at assuring to the patients, as much as possible, the best HRQoL, strictly depending on their psychological well-being and on their ability to perform daily and social activities.

Based on this evidence, the evaluation of MDs and HRQoL, the investigation of their main determinants and of the interplay between both, is not only mandatory to allow an unbiased evaluation of patient's cancer care outcomes but might be considered as early independent predictors of survival (Mauer 2007).

This thesis is part of an ongoing project that aims to investigate the prevalence and the association of MD with the specific clinical and anatomical features related to the tumour itself and with the patients' cognitive outcome both aimed at disclosing the influence of Cognitive and Mood disorder on HRQoL in patients with brain tumour. Results of this study will allow, as main clinical impact, to develop specific "interventions" aimed at improving the HRQoL of brain tumor population.

The thesis is organized in 7 Chapters. The first section, Chapters I-II-III, provides the basic background on the Cognitive functions and of Neuropsychological assessment (Chapter I), on brain tumour -diagnosis, symptoms and treatments- (Chapter II) and on the Cognitive and Mood disorders affecting specifically patients with brain tumour focusing on the role of the neuropsychological approach in neurosurgery, aimed at providing useful tools to increase the extent of resection while preserving neurological and cognitive functions, ultimately affecting the HRQoL

of patients. In the second section the main comprehensive aim of the study and the materials and methods commonly adopted in all the research studies are reported (Chapter IV) while the specific premises, methods and results for the different studies reported will be reported in the individual chapters (Chapters V, VI, VII). In particular Chapter V reports the experimental results relative to the assessment of the MD and the effect of the MD on the HRQoL in a large cohort of Brain tumour patients. Chapter VI and VII report the feasibility, accuracy and efficacy of two new intra-operative tools designed to preserve specific functions -attentive/executive and visual field capabilities respectively- found to be significantly and specifically associated to the emergence of MD, worsening the HRQoL, in brain tumour patients. The discussion of the results is reported for each study separately and a general discussion and conclusion is reported at the end of the study.

# *SECTION 1: BACKGROUND*

# *CHAPTER I*
# *COGNITIVE FUNCTIONS*

The human brain is one of the most complex systems in the natural world. We can consider the brain as a "machine", finely adjusted by natural evolution to enhance adaptive behaviors that allow the survival and reproduction of organisms. Humans must adapt not only in the physical but also the social environment, where the interaction with other individuals, with different beliefs and cultural habits, is unavoidable and where the technological abilities are mandatory for a correct interaction. Human cognition can be indeed considered the product of a gradual 'co-evolution' occurred when selection pressures favored the evolution of both technical and social skills (e.g. tool making and cooperation).

The progressively (exponential) growing cultural complexity and technological progress over time, forced the human brain to grow and to increase its internal architecture to "accommodate" the environmental changes. In particular the development of an increasingly complex social life led to the development of progressively more complex cognitive abilities such as a language and theory of mind: the technological sophistication, the capacity for introspection, and the ability to create and manipulate tools and symbols became unique abilities distinguishing humans from all other animals.

According to the definition by Neisser, (1967), the word "cognition" refers to the "*mental process by which external or internal input is transformed, elaborated, stored, recovered and used*". Humans use cognition to acquire knowledge and to understand the environment through senses, experience and thoughts. Cognition is used to guide behavior, in that it enables to perceive and react, process and understand, store and retrieve information, make decisions and generate appropriate responses/behaviors to interact with the world more adequately and effectively. Cognition is not an unitary process, but it is generated by the interplay of multiple distinct processes subserving a variety of functions such as perception, attention, memory coding, retention, and recall, decision-making, reasoning, problem-solving, imaging, planning and executing actions.

## *1.1 THE MAIN COGNITIVE FUNCTIONS*

Brain cognition emerges from different interrelated processes/functions that work together synergistically to integrate knowledge to organize and regulate specific behaviors. The term "superior cognitive processes" specifically refers to the following functions:

- *Attention*

Attention is the ability used to elaborate the incoming information or stimuli reaching the brain simultaneously, from the external (e.g. smell, sound, images) or from the internal (e.g. emotion, thoughts) environment, on the basis of their relevance for our purposes or their perceptive salience (Petersen et al. 1990; 2012). The attentive function encompasses different processes allowing us not only to select the target stimuli by inhibiting distractions or temptations (*selective attention*) but also to maintain an effective state of concentration over a period of time (*sustained attention*) and to respond to more than one task at a time or do two things at once (*divided attention*) (Lezak, 2012). Attentional deficits can affect negatively/impair all the cognitive functions.

- *Memory*

Memory is the ability to store information that can be retrieved when necessary. Memory is a complex function involving different subcomponents that play specific functions. Memory allows to storing different types of information for different periods of time. Based on the types/nature of the stored information, or based on the length of the memories, it is possible to distinguish between verbal and visuospatial memory, as well as between long-term memory, which refers to permanent storage, and short-term/immediate memory, storing information in the range of seconds to one or two minutes. Long-term memory is divided into explicit (conscious or declarative) and implicit (unconscious or procedural) memory. By the explicit memory the stored information are consciously recalled while implicit memory refers to more heterogeneous abilities, such as priming, skill learning, procedural memory and habit formation (Strauss et al. 2006). If the attentional system fails to work properly, memory is impaired in that we will not be efficient, and we'll fail to code, store, or recover the stored information.

- *Language*

Language is a symbolic communication system important for communicating with others and for structuring our internal thoughts. Language function refers both to the ability to communicate verbally through symbols (writing abilities), and to the ability to understand verbal and writing messages. Language deficits or aphasia are acquired impairments in

language production and comprehension, resulting in inabilities in speaking, listening, understanding reading, writing and gesturing (Hillis 2007).

- *Perceptual abilities*

The perceptual functions refer to activities such as orientation, awareness, recognition, and discrimination of different elements of the world through the different sensory modalities i.e. through the visual system, the sense of touch or the acustic system. Impairments in perceptual integration lead in disorders of recognition, classically known as the "agnosias" (Lezak, 2012).

- *Visuo-spatial and constructional abilities*

Visuospatial function refers to the ability to process, interpret and understand the visual information about objects in space and their spatial relationships, including the capacity to represent, analyze, and mentally manipulate objects. The term "spatial" refers also to our capacities in perceiving space, distance, and direction. These abilities play an important role in a wide range of activities of daily living such as for accurately reaching for objects in the visual field, to move around and be oriented in the environment appropriately. Constructional ability refers to the capacity in assembling, building and drawing spatial form (Benton 1969).

- *Praxis functions*

Praxis abilities are defined as finalized, intentional, goal-directed motor behavior (Le Gall et al., 2012). Gesture is essential for human social interactions with the peers and the environment to predict a social partner's action and to participate in playing and social activities like sports or video-games (Meltzoff and Decety, 2003). According to the main literature, praxis deficits encompass a wide spectrum of higher-order motor disorders, resulting from acquired disease, affecting several domains of learned motor behaviors such as imitation of meaningless gestures, symbolic expressive gestures (communicative or pantomimes) and real tool use (De Renzi et al., 1982; Goldenberg et al., 2009). Importantly praxis deficits occur in patients showing adequate comprehension of the element and the goals of the required activity and, importantly, in absence of motor and/or sensorimotor deficits.

- *Executive functions*

Executive function is a complex set of processes including cognitive flexibility, planning, judgment, decision-making, initiation, and hypothesis generation (Strauss et al. 2006). Generally, the executive functions control and direct lower-level abilities in order to produce goal-directed behaviors. In novel situations, where no previously learned routines are of use, executive functions contribute to the development of new strategies and monitor their effectiveness. Dysfunction of executive functions might lead in inappropriate social behaviors,

problems in showing good judgement when there is a need to change plans, difficulties in initiation, organizing and following plans, difficulties in generating strategies and in correcting errors using environmental feedback (Strauss et al. 2006).

Across human lifespan the cognitive functions, underpinned by both genetic and environmental factors, are constantly developing, changing and adapting to process new information, regulating our behavior.

## *1.2 LOCALIZATION OF THE FUNCTIONS: THE "BRAIN NETWORK"*

Cognition and the resulting behaviors can be conceptualized as "products" of the brain. The human brain is a complex "information processor" capable of generating and integrating information from multiple external and internal sources in real time. Nowadays it is acquired knowledge, and considered obvious, that the cognitive functions are generated within the brain, composed by the neurons connected in circuits computing the neural processes resulting in neurological functions. However, the path of knowledge leading to the awareness of the relationship between body and "mind" has been long. Among the first to explicitly emphasize the relationship between mind and body, was Descartes in the 17th century. Descartes considered the animals and humans as a machine, created by God, and believed that their functions were the result of the activity of a complex mechanism supported by the coordinated motion of individual gears. The vegetative functions, motor and sensory, in his opinion, were not "implemented" by some faculties of the soul but were merely needed to actuate the operations of the mechanical system. According to Dualism theory the reality was composed by two different substances, the "*res extensa*", i.e. the body, and the "*res cogitans*", i.e. the mind, thoughts and reason. The *res cogitans*, the manifestations of the soul separate from the body and ontologically distinguished by *res extensa*, were believed to be exclusive prerogative of man. The *res cogitans* and *extensa* were connected in a precise structure of the brain i.e. the pineal gland, a structure that, in the Cartesian mechanical system, represented the nervous center of sensation and movement.

In the second half of the XVII century, the Dualism theory was strongly criticized by many doctors and anatomists who demonstrated, with the aid of the microscope, that the hypotheses advanced by Descartes were wrong. However, at the end of the XVIII century, despite the significant evidence provided by studies investigating the macroscopic anatomy of the nervous system (all identified and described in its main parts), the mechanisms and the structures underlying the mental functions remained obscure. The strong belief that the cognitive processes - according to the Cartesian

dualism and to the materialist approach - were the pure manifestation of a mind or soul, separate from the body in contact with the body through a specific cerebral and indeterminate structure, was not challenged by the discovery of the brain.

Only in the XIX and XX centuries it was finally accepted the hypothesis suggesting the cerebral cortex as the structure responsible for control and of the coordination of the behavior and cognition leading in the "*phrenology*" theory, proposed by Gall (Gall et al. 1835). According to phrenology the cerebral cortex was divided into separate areas each one subserving different cognitive functions. The novel aspect of this theory was the main concept that the cognitive functions were not generated by an immaterial soul to be distinct from the body, but they were rather intrinsically generated by a corporeal structure, the brain. The map of the cerebral cortex representing the different functions in different areas of the cortex resulted from the correlation between the behavior of some individuals and their shape of the skull, based on the hypothesis of a strict association between the cognitive functions more developed in a given individual and the cortical areas more expanded in the same subjects and thus reasonably subserving those functions (Fig.1). Although the phrenology theory was then proved to be scientifically unfounded, it was a brilliant intuition providing the precursor foundation for the concept of the cortical networks subserving different neurological functions.

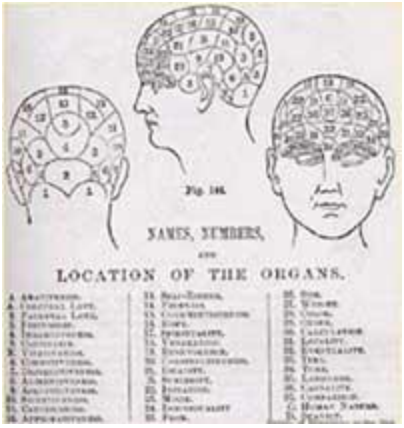


*Fig. 1. Phrenological schema*

Opponents of this theory, the physiologist Flourens (1794-1876) and Goltz (1832-1902) argued, on the contrary, for a more holistic view of the functioning of the brain. Specifically, Flourens, performing anatomical studies in birds, described that the consequence of the lesions experimentally induced in specific areas of the brain were not permanent deficit, because in a short time the birds recovered the functions they had temporarily lost. According to these observations he

was convinced that sensations, perceptions, movements were the functional expression of the brain as a whole entirety.

The holistic theory was significantly challenged in the second part of the XIX centuries with the progressive emergence of pathological anatomy. The approach of this discipline, promoted above all in France by the physiologist and pathologist Claude Bernard (1813-1878), aimed at investigating the correlation between lesions or degenerative processes of different organs with the alterations of specific physiological processes. In this period the anatomo-pathologist Broca (1824-1880) demonstrated the plausibility of phrenology theories, showing that lesion of a specific brain area (the posterior part of the left inferior frontal gyrus now called Broca's area) produced disturbances in the production of language. Paul Broca, based on the observation of the lesions, correlated the lesions of the left hemisphere, in the majority of cases, to language deficits and, despite the anatomical similarity of the two hemispheres (right and left) he suggested that the two hemispheres were actually specialized for different functions (lateralization of the hemispheres). For the first time, a specific cognitive function (language) was localized to a specific area (and hemisphere) of the cortex. In the same time Meynert (1833–92) classified the fibers of white matter for the first time, into "associative" bundles (connecting local and distant regions within the same cerebral hemisphere), "projection" (ascending and descending, such as pyramidal tract and cortical thalamic bundles) and "interhemispheric connections" (like the corpus callosum). This evidence founded the scientific background on which the "associationist theory" of Wernicke (1840-1905) and Lichtheim (1845-1928) developed. According to this theory, the neurological/cognitive functions were not localized in specific area, but rather they resulted from the activity of networks connecting areas hosting the sensory and motor memory images by means of associative connections.

Based on the clinical and scientific observations of Broca and other scientists, e.g. Wernicke, there was increasingly consensus on the idea that multiple and specific areas of the brain and their connections were related to specific behaviors and that, consequently, injuries or degenerative processes affecting these networks resulted in deficits in specific cognitive processes, such as language, memory and learning. Studies investigating the correlation between brain structure and functions were performed mainly into the medical field, forced by clinical needs. In fact, it was in these years that Wilder Penfield (1891-1976) disclosed the map of motor and somatosensory function on the cerebral cortex. Through electric stimulation of the brain Penfield disclosed the so-called "somatosensory and motor homunculus": by using electrical stimulation in a large group of epileptic patients undergoing surgery, he identified the precentral and postcentral cortical regions

related to motor and sensory function of specific body segments (hands, torso, feet, etc.). The psychologist Donald O. Hebb in his book "*The organization of behavior*" (1949), theorized that complex cognitive behavior could be as well produced by networks of active neurons. The mutual interaction between brain and behavior is, nowadays, a fundamental assumption of neuroscience: one structure influences the other and vice versa, and this influence is exerted through the so-called neural plasticity, i.e. the ability of brain structures to modify, both during development and in adults, their structure and functions driven by the different experiences acquired in life. In fact, although single regions of the nervous system are not fully and exclusively in charge of the execution of the different cognitive functions, as the phrenologists claimed, with the "disconnection theory" proposed by Geschwind in 1965 (Geschwind 2010) it was established, inexorably, that the cognitive faculties result from the interaction of many brain networks distributed in different parts of the brain and connected among them by associative fibers. From these assumptions originated the hodological mechanism, suggesting that dysfunction of cognitive faculties might be caused not only by lesions affecting the cortex, but also by lesions involving the white matter fibres as cortico-cortical or cortico-subcortical disconnection, hyperconnection or both. Modern neuroimaging technology as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and diffusion imaging (DI) combined with neuropsychological assessments, nowadays allow to investigate with high resolution the cortical and subcortical anatomo-functional mechanisms underlying cognitive functions. The evidence coming from studies based on diffusion tractography led to more hodological theories (Catani et al. 2005). The word "hodotopia" includes both "topos" aspects (i.e. localization), to indicate the brain network of primary importance for a given specific function, and "hodos" aspects (i.e. roads-paths) to indicate the connections between the structures involved. According to this model, the brain network is constituted by different neuronal populations distributed in cortical areas, which are connected by short U-fibers or long fibers that, in turn, connect the network with other networks in parallel way, allowing for functional integrity (Fig. 2).

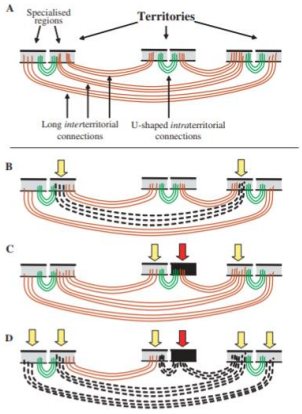


*Fig. 2 : A hodotopic framework for clinicopathological correlations (reproduced from Catani et al. 2005)*

The increasing anatomical evidence and the application of sophisticated functional brain modelling allowed to study the architecture of brain organization with new methods based on the identification of several highly connected central hub regions (nodes, spokes, hubs, etc.) based on functional MRI at rest, where changes in blood oxygenation (BOLD) in different regions has been measured to be temporally cohesive, indicating a functional correspondence with specific functions. This has led to the more recent model suggesting that these network hubs, hierarchically organized, and their connections, play key roles in the integration of information and in efficient neuronal signaling and communication in the brain (Theory of connectome) (van Den Heuvel et al. 2012; 2013; Sporns 2013). In this light, the cognitive functioning depends on a perfect functional interplay and synergy between the cortical areas, the deep brain structures and the white matter bundles wiring very complex networks.

## *1.3 ASSESSMENT OF COGNITIVE FUNCTIONS: THE NEUROPSYCHOLOGY*

As previously described, current knowledge about the functioning of brain activity arises from clinical observations that unrevealed direct associations between specific cognitive impairments and brain injuries to specific brain structures: the lesion of a specific cerebral region results in a particular deficit leading to the conclusion that, generally speaking, the different cognitive functions are sub served by distinct and separate networks in the brain. From the anatomo-clinical correlation method emerged the development of modern neuropsychology. The term neuropsychology is indeed defined as the performance-based study/assessment of the cognitive and emotional deficits caused by lesions o dysfunctions of the central nervous system (CNS). This relatively recent discipline originated in the attempts of physicians in the late XIX and

early XX centuries to evaluate the mental abilities of patients with brain disease (at the beginning focusing particularly on aphasics and people and servicemen during the first World War) with a higher clinical/diagnostic resolution with respect to the blurred evaluation accomplished by the clinical description available at that period.

From the methodological point of view, the neuropsychological method developed and improved in time. Initially it was focused on the study of cases of patients clearly showing specific deficits. As main limitation at that time, the method neglected all the so-called "negative cases" i.e. those patients who, although affected by brain injury, did not show clear deficits. Moreover, at the beginning, patients' performance was not evaluated with a quantitative method and, importantly, it was not compared with a population of neurologically healthy subjects (control groups). Starting from the second half of the last century, both in Europe and in the United States, the method evolved from the simple, though detailed, descriptions of clinical cases, to the detailed analyses of patient performance evaluated with specific tests (Benton 2000). Neuropsychological assessment became a performance-based method using pencil and paper tasks (Tests) to assess a variety of cognitive ability areas. The tests are now structured to require individuals to exercise their skills under the inspection of an examiner/observer. The emergence of the first tests raised the need to quantify the patient's performance and, importantly, to compare the scores measured on patients with the scores measured on healthy people, i.e. the normative comparison. By the normative comparison the performance of an individual at the time of the test must be compared to the performance of reference groups of healthy subjects with the same age, sex, race, and educational level. The normative comparisons is mandatory to evaluate whether an individual is performing as expected, considered his/her lifetime levels of achievements, and educational attainment, or if the performance is poorer than expected, and thus the individual falls in pathologic scores.

With the availability of the innovative high-resolution neuroradiological techniques, the neuropsychological assessment is no more needed to infer the site of brain lesions, however the neuropsychological testing is still crucial for other and different purposes.

Firstly, neuropsychological assessment is useful for *"Diagnostic aims"* in that it allows to discriminating between psychiatric and neurological symptoms, to distinguishing between different neurological conditions, to understanding the efficiency of the patients in all the different cognitive areas and to monitoring their efficiency over time. In some cases, it is an essential diagnostic tool, for example in mild traumatic brain injury or in cognitive impairment in which no apparent lesions can be detected with instrumental tools and the only diagnostic evidence is the neuropsychological evaluation. The neuropsychological assessment is of great aid in prodromal or early detection and

prediction of dementing disorders (Seidman et al., 2010). In patients with intractable epilepsy, neuropsychological evaluations are critical for identifying candidates for surgery as well as for implementing postsurgical programs (Baxendale and Thompson, 2010; Jones-Gotman Smith et al., 2010).

Related and consequent to the diagnostic aims, is the "*Prognostic aim*": the neuropsychological assessment provides elements useful to predict the gravity of neural deficits following traumatic brain injury or in case of brain tumors.

The neuropsychological method is of great aid also in "*Patients care and planning*". For patients, and for their caregivers, is important to understand how the disease changed their behavior and how the cognitive deficits affected their abilities to manage the everyday life activities. In many cases, the neuropsychological assessment provides an objective evaluation about the patients' capacity for self-care, the patient's reliability in following a pharmacological treatment, the patient's capacity to perform activities of daily living such as driving etc. All the data of the neuropsychological examination (patient's history, background, qualitative observations, and quantitative scores) allow a neuropsychologist to gain a realistic estimation of the patient's reaction to his/her deficits and a prediction regarding whether and how the deficits can be compensated (Diller, 2000; Sohlberg and Mateer, 2001).

Finally, the neuropsychological method contributes to "*designing and planning individualised treatment programmes*" aimed at restoring or compensating the functional deficits and identifying the residual skills at the same time. In this specific context the neuropsychological assessment allows us to monitor the rehabilitation program or the efficacy of the pharmacological and/or surgical treatment.

Irrespectively to the aim of the neuropsychological evaluation, in order to obtain a valid measure of the cognitive efficiency it is not sufficient to administer tests that have good normative data to be compared with the scores of the subjects evaluated, but it is mandatory to conduct specific observations in order to understand the actual patient's conditions. In fact, the execution and interpretation of tests is only part of the neuropsychological evaluation to be completed with two other important assessments. The first assessment is the "clinical interview with the patient and his/her caregivers", that precedes the formal testing, during which the examiner explores the functional daily living abilities and the possible perception of the patient himself or his relatives about cognitive change and their impact in real life. Second, during the formal evaluation the examiner has the opportunity to observe the interaction modalities of the patient and the possible evidence/occurrence of qualitative pathological index; in fact, there are some contextual or clinical

variable that have to be taken seriously into consideration during cognitive assessment, because they can interfere with cognitive functioning.

As a general consideration it can be concluded that the neuropsychological assessment is a method aimed at evaluating brain functions by studying its behavioral product; the performance and symptoms may indeed reflect the disruptions of an organized, distributed network of structures that sub serving the specific investigated functions.

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# *CHAPTER II*
# *BRAIN TUMORS: DEFINITION, DIAGNOSIS, SYMPTOMS AND TREATMENTS.*

Primary Brain Tumour is an infiltrating, expansive chronic disease harbouring within the central nervous system (CNS) caused by an abnormal and uncontrolled proliferation of cells. Due to the limited space inside the skull, brain tumour growth increases intracranial pressure, and may cause edema, reduced blood flow, and displacement, with consequent degeneration, of the healthy brain tissue that controls vital functions. Primary brain tumors do not show a metastatic behavior in that they do spread to other body sites outside the CNS. Primary brain tumours are classified as malignant or benign based on their histology, molecular parameters and histological grade.

Primary brain tumours include several histologic types with different gross and molecular characteristics and are classified based on the World Health Organization (WHO) classification of tumours of the CNS (Louis et al. 2016). According to the WHO grading scheme CNS tumours can be stratified by degree of malignancy from the least to the most aggressive. The grading of malignancy is based, principally, on the following aspects of tumours: nuclear atypia, mitotic activity, cellularity, vascular proliferation and necrosis.

- **Grade I**: lesions with low proliferative potential i.e. slow growing (*low grade glioma -LGG*) Surgical resection is the main treatment. Within this category are included some histotype of low-grade astrocytomas, such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma
- **Grade II**: infiltrative neoplasms with low proliferative activity *(LGG)*, but with the tendency to recur after surgical treatment and always to progress to a higher grade. This category includes infiltrating neoplasms such protoplasmic astrocytoma and, olygodendroglioma.
- **Grade III**: lesions with histological evidence of malignancy and faster growing *(high grade glioma HGG*). This category includes anaplastic astrocytoma and anaplastic oligodendroglioma, which is one of the most common primary malignant brain tumours in adults (Martin et al. 2017).
- **Grade IV**: cytologically malignant fatal neoplasms with rapid evolution (*HGG*), these lesions grow and spread quickly; this category includes glioblastoma (the most lethal brain tumour), gliosarcoma and giant cell glioblastoma (all included in glioblastoma).

All CNS tumours are considered a rare disease. Data from "*Surveillance of Rare Cancers in Europe*" (*RARECARE, 2012* - the analysis considered case incidents from 1995 to 2002) and "*Associazione Italiana Registro Tumori*" (AIRTUM, 2016) showed that the rate of incidence corresponds to about 6 cases per 100000 people/year in Europe, and 5.89 per 100000 people/year in Italy. CNS tumours affect more males than females (M/F ratio ranging from 1.14 to 1.81), with the sole exception of malignant meningiomas (M/F: 0.81). The most frequent histotype is the astrocytoma, which accounts for 83% of the total, followed by oligodendroglial tumours (6.4%), ependymal and embryonal tumours (both at 3.9%) and malignant meningiomas (2.3%). Incidence of all tumours tends to increase after age 40 years, with a peak in the 65-75-year age group; however, astrocytomas and embryonal tumours also occur in young children (AIRTUM, 2016).

## *2.1 PREVALENCE*

Gliomas are the most common primary brain tumour affecting adult population. Considering all the diagnosed primary brain tumours, according to the Central Brain Tumour Registry of United States (CBTRUS – Ostrom et al. 2018) statistical report, approximately 67% are non-malignant. The most common histology of all primary malignant CNS tumours is glioblastoma. Gliomas account for 27% of all CNS tumours and 80% of malignant tumours. The localization of brain tumour is age-dependent: in adults the 80% of primary malignancies are supratentorial, while in children 60% are infratentorial. Considering the distribution by site, malignant tumours most commonly affect the cerebrum (> 54% of cases), and, more precisely, in decreasing order of incidence, the frontal, the temporal, the parietal, and the occipital lobe. Other relatively common sites include the cerebellum (4.5%), the brainstem (3.6%), and the spinal cord (3%). Considering the non-malignant tumours, about the 53% occur in the meninges (AIRTUM, 2016).

## *2.2 SURVIVAL AND PROGNOSTIC FACTORS*

Based on the collected data by the RARECARE in Europe, the survival was longer for 'non-glial tumours of CNS and pineal gland' (601 cases analysed) than for 'glial tumours of CNS' (13,667 cases). For all the CNS tumours the survival at one year and at five years is 55% and 21%, respectively (AIRTUM, 2016). Within all glial tumours, the ependymal tumours have the best 5-year prognosis (74% overall, 80% low grade and 37% high grade). Intermediate prognosis was reported for oligodendroglial tumours (55% overall; 65% low grade and 30% high grade), while

short survival was estimated for astrocytic tumours (15% overall; 4.9% for high grade; 43% for low grade tumours) (Crocetti et al. 2012). The difference in the percentage of survival among the different histotypes of brain tumours might be partially explained by the different proportion of the HGG within each histotype and by their molecular profile; in fact, ependymal tumour includes the 82% of the LGG (WHO I and II grade); oligodendroglial includes the 72% of the LGG while the astrocytomas include an higher proportion (64%) of the HGG (WHO IV grade) and specifically of glioblastoma (AERTUM, 2016). For glial tumours five-year survival was slightly higher for women (20.7%; 95% confidence interval 19.6–21.9) than for men (18.7%; 95% CI 17.8–19.7). Overall, 5-year survival is valuable for children and adolescents (0–19 years; 58.1%), and for young adults (20–39 years; 52.8.0%) and decreased steadily for adults (40–59 years; 19.1%), and especially for older subjects (60+ years; 4.4%) (Crocetti et al. 2012).

Based on this data and on the most recent–studies performed over the past decade, the factors significantly impacting on the patient's prognosis are (Bauman et al. 1999; Pignatti et al. 2002; Gorlia et al. 2008; Huse et al. 2015; Stupp et al. 2003):

- **Grade and Molecular features**: overall LGG has better prognosis than HGG. However, within each group, specific genetic mutations found in the tumour cells must be considered to determine the prognosis. These mutations include: IDH1, IDH2, MGMT, and a 1p/19q co-deletion. Specifically, tumours with mutated IDH and codeleted 1p19q show a better prognosis than tumours with mutated IDH and without 1p19q codeletion (8 years vs 6.3 years); wild types IDH show a median survival of 1.7 years, which is lower than the median survival of patients diagnosed with Grade IV IDH mutated Glioblastoma.
- **Age**: when considering tumours affecting adults, the age is significant factors affecting the prognosis. In general, younger adults have better prognosis.
- **Symptoms:** The evidence and a long history of symptoms seem to be prognostic factors. For example, occurrence of seizures and a long-time history of symptoms, possibly indicating a slow tumour growth, correlate with a better prognosis. The absence of symptoms (incidental discovery) also correlated with a better prognosis.
- **Extent of tumour residual**: At present surgery is one of the treatments impacting on the prognosis, and its effect seems to be independent upon tumour grade. The term "residual" refers to the amount of tumour tissue left in surgical site the after surgery. The prognosis is correlated to the percentage of the whole tumour mass resected, the higher the percentage correlating with a better prognosis.

- **Tumour location**: the localization of the tumour also impacts on the prognosis in that it affects the feasibility of the resection brain tumours diffusively infiltrated or located in brain regions hardly approached by the surgical resection lead in a bad prognosis, associated with severe neurological deficits and progression shortly after the diagnosis.

## *2.3 DIAGNOSIS*

Among the brain tumours, the LGG remains silent for a long time to such an extent that the diagnosis may be an incidental finding in the setting of imaging procedures performed for different reasons (e.g. a minor trauma or persistent headache), while the HGG typically occurs with subacute and progressive neurologic signs evolving over the course of days to weeks. The diagnosis of brain tumour is first assessed with specific brain imaging investigation followed by histopathology to confirm the specific diagnosis (see above).

Several brain imaging is currently used for brain tumour diagnosis: Computed Scan (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomografy (PET). These techniques provide different information useful both to the diagnosis and planning of treatment i.e. the location and size of the tumor (MRI), the occurrence of cerebral edema, features predictive of tumour grading, delineation of tumor margins and to the follow up of patients i.e. the response to therapy and tumor progression or tumor recurrence. Due to its higher resolution, the MRI must be preferred to the CT scan for the characterization of the lesions and as a more accurate guide for surgical resection. In fact, MRI provides morphological images, namely T1-weighted sequences with Gadolinium, T2 and FLAIR sequences, allowing the evaluation of the tumor's location, volume and anatomical relation with the adjacent structures. The neuroradiological study provides the morphologic characteristics of the lesion and, when specific techniques as the Functional Magnetic Resonance (fMRI) and Diffusion Tensor Imaging (DTI) are available, might be of help in planning surgery. Specifically, the fMRI, by detecting changes in the neuronal activity induced by motor or cognitive tasks when applied to patients affected by brain tumour, provides information about the location of the brain areas actively involved in a specific task and thus functionally spared by the tumour which, conversely, is not responsive. Not fully reliable for surgical guidance, this technique provides elements useful to identify the cortical areas to be preserved by surgery, although its impact at individual patient level is quite limited. The DTI allows to reconstruct the white matter tracts connecting the different part of the neural network in the brain, tracking the orientation of the axons running in the white matter fibers, and, therefore, in describing the trajectories of the tracts

and their modifications induced by the lesions. This is important in the evaluation of the brain lesion in that the tumor, during its growth especially at subcortical level, affects the adjacent fibers structure causing disruption, displacement or infiltration of the fibers (Wei et al. 2007; Berman et al, 2009; Bello et al. 2008). However, also the usefulness of DTI at individual patient level is quite limited.

## *2.4 SYMPTOMS*

Brain tumours can cause direct or indirect damages due to the infiltration of the brain tissue or due to the effect of the mass increasing the pressure on the brain structures. These damages might cause generalized and/or focal symptoms depending on the volume of the tumor mass and its localization. These symptoms can occur at different stage of the tumours depending on the histotype of the tumoral mass. In fact, as stated above, the LGG may remain clinically silent for years because grow very slowly, while the HGG develop subacute and progressive neurologic signs over the course of days to weeks. Typically, generalized symptoms can be caused by the pressure of the mass on the brain structure while focal ~~are~~ can be caused by the direct impairment due to the tumours infiltration, compression or induction of dysplastic alteration of the specific structures of the brain.

Generalized symptoms include:

-*Headache*: this sign is not caused directly by the tumor itself but is due to the increasing pressure acting on pain-sensitive blood vessels, cranial/cervical nerves and meninges. The increasing pressure can be due to the direct compression of cranial and cervical nerve fibers or to the block of the flow of cerebrospinal fluid within the brain by the tumor itself. Severe headache is the most common presentation symptom among glioma patients (46% of patients) and it is usually dull, constant and worsening with changes in body position -such as bending over- or with manoeuvres increasing the intrathoracic pressure -such as coughing or sneezing-. Headache is a common symptom, often associated (especially when due to intracranial pressure increase) with other warning cues as nausea and vomiting and an abnormal neurological signs.

-*Seizures*: referred to as 'fits', seizures are the second most common presentation symptom (33% of patients). Seizures may be more common in LGG (more than 80% of patients) (Pallud 2014) specifically in patients with oligodendroglial tumours, which tend to involve the cortex, and when the lesion is located in the temporal lobe, the insula, the supplementary motor, and ventral pre-motor areas (Lee 2010), and in older patients (aged ≥ 50-60 y). Seizures are alterations of the

electrical activity of the cortex, due to an uncontrolled synchronous discharge of populations of neurons. Seizures can be “focal”, with or without altered awareness, “generalized tonic-clonic seizures” (when the discharge involves both hemispheres) or “focal with secondary generalization”. Severe seizures can cause to loos of consciousness, while subtle seizure, which are more commune than severe, can cause symptoms such as muscles spasm, change in sensation, vision, smell, and/or hearing and can be associated with different neurological signs varying with tumour location.

- *Nausea and vomiting* are aspecific symptoms present in 22% of patients, generally caused by the increased intracranial pressure at the area postrema of the medulla. Neurogenic nausea and vomiting usually occur in the context of other neurologic symptoms such as headache or focal neurologic deficit.

-*Focal symptoms*: *limbs and face muscle weakness*, present in 25% of patients; *limbs and head paraesthesia*, in 16% of cases referred to the head, and 9% to the upper limb (*hand paraesthesia).* *Visual disturbances* are reported by 25% of patients reporting blurred or double vision or visual filed defect.

-*Cognitive and psychological disorders:* focal neuronal lesion, mass effects and alterations of brain connectivity induced by the tumour, due to the disruption of the neural circuits subserving cognitive functions (see Chapter I) and behaviour, often cause cognitive deficit and behavioural alterations. The nature of the deficit depends, mainly, on the severity and localization of the tumour. Rapidly progressive tumours (HGG) such as glioblastoma may show up with acute cognitive symptoms related to the abrupt increase of intracranial pressure or to vascular lesions, while slow growing tumours (LGG) may have a more extensive brain infiltration but with subtle or minimal acute cognitive symptoms, often masked (or underestimated) as part of underlying personality. Based on the laterality of the localisation, right hemispheric or *non-dominant* lobe tumour can cause deficits relating to visuo-spatial attention and executive functions. Left hemispheric or *dominant* lobe lesions are more likely to result in apraxia and expressive and receptive aphasia. However, there are other potential factors related to the aetiology of cognitive deficits such as treatment-related endocrine dysfunction, mood disorders and anti epileptic drugs (AED). Certainly, with respect to the older AEDs (phenobarbitone, phenytoin, carbamazepine and valproic acid) proved to decrease neurocognitive functioning by impairing attention and memory, the newest AEDs, namely gabapentin, lamotrigine and levetiracetam, show fewer adverse neurocognitive effects (for a detailed discussion, see the chapter III).

## *2.6 TREATMENT*

Treatment of brain tumours is based on surgery, radiotherapy or chemotherapy. The main goal of the treatment is both symptom alleviation and prolongation of survival. The association of the different treatments depends on different factors and mainly the histological diagnosis, location and size of the tumour, patient's age and general state of health. However, independently of the diagnosis (LGG or HGG), when feasible, the surgical resection remains the primary and the gold standard treatment (for details see section 2.6.1 and Chapter III). According with the new WHO brain tumour classification (2016) integrating histo-morphological and molecular parameters for the diagnosis of primary brain tumours, different genetic subtypes of morphologically identical tumours have different natural histories and may differ significantly in their response to treatment. For this reason, based on the histological and molecular parameters, the surgical resection of the tumours it is followed by different adjuvant treatments: radiotherapy (RT) or chemotherapy (CHT) (for details see section 2.6.2).

### *2.6.1 SURGICAL TREATMENT*

At present, the surgical resection of the tumour mass is one of the most important treatment impacting on the natural history of the brain tumour (Schmidt et al. 2003). Surgical resection decreases the mass effect on the nervous structures, decreases the intracranial pressure, impacts on patient's survival and, notably, provides the biologic material for histologic and molecular diagnosis. The indication for surgical resection must be based on the general and specific clinical status of the patient and on the neuroradiological investigations. The main contraindications to surgery are diffuse brainstem tumours, especially those located in the pons, advanced age (usually > 70 years) when considering the comprehensive clinical profile of the patient, a low Karnofsky performance status (< 70%), multiple tumour localizations and involvement of the corpus callosum with contralateral extension and involvement of the basal ganglia.

However, modern neurosurgery methods like optical microscopy, the ultrasound aspiration (which allows for parenchymal removal whilst conserving the vessels), the stereotactic modalities, neuro-navigation systems (to estimate the surgery target) and brain mapping techniques (see Chapter III for details) allow to reduce the amplitude of the craniotomy, to minimize the risk of postoperative permanent deficit maximizing the extent of resection (EOR). In particular, total or supratotal surgical resection, when possible, is indicated as the first therapeutic option to adopt because it was

demonstrated effective in improving seizure control, progression free survival and overall survivor, all while reducing the risk of malignant transformation (in LGG patients) and dramatically changing the natural history of the tumour (Soffietti et al. 2010).

### *2.6.2 ADJUVANT TREATMENT: RADIOTHERAPY AND CHEMOTHERAPY*

Radiotherapy is a specific treatment that uses high-energy ionizing radiation (a beam of penetrating photons, of 5-10 MeV of energy) aimed at destroying the tumour cells by damaging their DNA, whilst causing the lowest possible damage to the surrounding healthy cells. Chemotherapy consists in the administration of cytotoxic (anti-cancer) drugs aimed at inhibiting the growth of tumour cells by impairing their duplication. A chemotherapy protocol used as the first line treatment for brain tumours is PCV (Procarbazine, Lomustine and Vincristine) or a new generation drug - Temozolomide (TMZ) - introduced in the clinical practice about 10 years ago. It is still unclear whether temozolomide is equally effective as PCV, and there are no randomized controlled trials that have compared these two regimens head-to-head in gliomas population. Both regimens seem to affect the gliomas but TMZ is generally preferred based upon its ease of administration (TMZ given for five days per month), better patient tolerance, and more consistent availability in some regions of the country.

As stated above, the approach to treatment of brain tumours depends, mainly, on the histo-molecular features of the tumoral mass (HGG vs LGG). Generally, the treatment strategies for HGG tumours include the surgical resection, as main treatment, followed by radiotherapy (administered immediately after surgery -20-30 days after- total dose is 60 Gy divided in 30 daily fractions) and chemotherapy. This "standard therapy" for patients with HGG tumours was established after the publication of a European prospective randomized study reported by Stupp and colleagues in 2005. They reported a significant survival benefit for patients with glioblastoma by adding chemotherapy, as described above, to the standard therapy at that time consisting exclusively of radiotherapy. These results are confirmed by recent studies, about elderly patients, showing that the addition of TMZ to radiotherapy extended the median overall survival of HGG patients from 7.6 months to 9.3 months (Perry et al. 2017).

Differently, for patients with LGG tumours, the treatment includes the surgical resection followed by watchful waiting in case of complete resection; in case of partial resection, and when no further surgery can be planned, radiotherapy and alkylating chemotherapy is indicated (Preusser et al. 2015). The choice to administer all these treatments and their combination in LGG patients is still controversial. However, recent studies showed that in LGG patients treated with biopsy or at least

partial resection the administration of radiotherapy alone lead to shorter survival with respect to cases receiving the additional chemotherapy (7.8 years vs 13.3 years) and that greater benefits was obtained for patients with 1p/19q codeletions and isocitrate dehydrogenase (IDH) mutations (Buckner et al. 2016). After a median follow-up of 48 months, patients with IDH1 mutation and 1p/19q codeletion had the longest period of progression-free survival (PFS) of 62 months (95% CI 41–not reached), followed by the patients showing IDH mutation only. In the EORTC trial 22033, patients with LGG were randomized to either radiotherapy or dose dense chemotherapy with TMZ when radiologic tumour progression or progression of symptoms occurred (Baumert et al. 2016). After a follow-up of 48 months, patients with IDH1 mutation and 1p/19q codeletion showed the longest period of progression-free survival (PFS) of 62 months, followed by the patients showing IDH mutation only (48 months, range 41–55 months), whereas patients with IDH wild-type had the shortest PFS of 20 months (range 12–26 months). IDH mutated, non-codeleted patients experienced a longer period of PFS with radiotherapy than with chemotherapy (55.4 vs 36 months).

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# *CHAPTER III*
# *COGNITIVE AND PSYCHOLOGICAL DISORDERS IN BRAIN TUMORS PATIENTS. NEUROPSYCHOLOGY AND NEUROSURGERY: A NEW SYNERGY FOR NEURO-ONCOLOGICAL PATIENT MANAGEMENT*

The human brain, with its own extraordinary complexity, is the organ that controls all our sensory, motor and cognitive functions. When a tumour is localized in the brain, it is important to take into account that a patient's cognitive and psychological functions can be affected. Cognitive and psychological disorders can lead in loss of functional independence such as an inability to undertake activities of daily living and/or to return to work, negatively impacting on the patient's quality of life (QoL) (Piil et al. 2013). For this reason, the aim of functional neuro-oncology is on one side to assure the best treatments for the patients with brain tumour according to the most modern techniques and therapies and, in the same time, to evaluate, preserve, rehabilitate the cognitive and psychological functions. For this reason, disciplines apparently distant from each other, like neurosurgery and neuropsychology, should work synergistically for the global management of the neuro-oncological patient and to guarantee the highest level of QoL.

## *3.1 COGNITIVE DEFICIT IN BRAIN TUMOURS*

Cognitive impairment, behavioural disturbance and difficulties in managing daily life are typical and frequent symptoms of patients with brain tumours. The prevalence of the deficits in at least one cognitive function associated with brain tumour, ranging from 29% in non-irradiated LGG patients to 90% in other different brain tumour groups (Tucha 2000; Meyers CA 2004). Probably, the reported differences in incidence of cognitive deficits may be partially due to differences in the patient's population studied, to the clinical variable related to the tumour treatment, to the neuropsychological tests adopted and to the conventional definition of impairment. Nevertheless, all factors considered, there is a clearly higher prevalence of cognitive deficits in patients with a brain tumour than in patients with extracranial cancers with a similar prognosis, suggesting specific risk factors associated with brain tumours (Klein et al. 2001). This observation might seem obvious, but in fact the exact pathophysiology of the cognitive impairment is still not clear. Several causes contribute to the development of cognitive deficits including, certainly, the direct effect of the tumour (location, size, progression and growth rate) and the tumour-related neurological

complications and/or its treatment. The cognitive disturbance may be due to a combination of all these factors.

Regarding the direct effect of the tumour mass, several studies reported that the tumour itself and its malignancy are the main cause of cognitive decline (Klein et al. 2002; Kayl et al. 2003; Bosma et al. 2003; Toucha et al. 2007). Cognitive dysfunction is observed more frequently at diagnosis in rapid-growing tumours such as HGG than in slow-growing ones such as LGG. Generally, LGG tumours can cause alterations in personality or Mood disorders, while HGG tumours have been reported to result more often in deficits in Cognitive function. However, the tumour type and its volume are not predictors of impairment. The set and the gravity of cognitive deficits seem indeed to be strongly associated with the tumour location and the therapy rather than with the tumour malignancy. Among HGG patients the intracranial hypertension seems to correlate significantly with cognitive deficits (Scheibel et al. 1996). However, irrespectively to the malignancy, tumours with different localizations and lateralization are associated with different patterns of dysfunctions. As described in Chapter I, cognitive functions are supported by neural networks connecting specific brain areas thus the infiltration of areas/connecting fibers belonging to these circuits is expected to lead to the impairment of one or more specific brain functions. Accordingly, frontal tumours are associated with deficits in working memory and executive functions, social cognition and flexibility, while tumours involving the anterior cingulate cortex are associated with attention and conflict monitoring deficits; tumours of the corpus callosum as well result in memory deficits; tumours in the temporal lobe lead in language and memory deficits; occipital-parietal tumours impair mainly visuospatial recognition, and visual deficits (Allegri et al. 1999; Taphoorn et al. 2004; Baird et al. 2006; Cappa et al. 2008; Giovagnoli 2012). Another relevant factor is the hemisphere affected by the lesion, due to the peculiar organization of brain functions preferentially lateralized in one hemisphere with respect to the other. Regarding lateralization, patients with gliomas in the dominant hemisphere (generally referring to the left hemisphere) show more cognitive deficits before treatment than those with non-dominant (generally referring to the right hemisphere) hemispheric lesions (Yoshii et al., 2008). Several studies have shown that left hemisphere tumours generally cause verbal deficits, while right hemisphere tumours are preferentially correlated to non-verbal disorders, such as visuospatial and abstract reasoning deficits. Overall, the deficits in cognitive functions related to damage in the left hemisphere are more serious and show poorer recovery than deficits due to lesions in the right hemisphere (Goldstein et al. 2004; Yoshii et al. 2008).

Aside to the direct effect of the tumour on brain circuits resulting in cognitive disfunctions (CD) also other factors related to the tumour acting on structural and functional connectivity may lead in cognitive impairment. In addition to the invasion of healthy brain tissue and growth rate effects, the compression due to oedema, the increased intracranial pressure, tumour-related seizures, also changes in sleep, psychological distress (Toucha et al. 2003) and tumour-related treatments (surgery, adjuvant, antiepileptics and corticosteroids therapy) can also contribute in determining the type and severity of cognitive impairment in brain tumour patients (Taphoorn et al. 2004). As explained in Chapter II, the treatment and management of cancer, especially the HGG, includes the combination of surgery, radio- and chemotherapy that may alleviate neurological deficits but can also have a cognitive side-effect. The disclosure of the individual contribute of the different treatments in the genesis of the Cognitive deficits is often not easy or not possible. These "indirect factors" can indeed disrupt the functionality of brain connectivity involving different neuronal networks, causing focal but also non-focal cognitive dysfunctions i.e. tumour-related cognitive deficits not restricted/confined to any single domain (Kahana M et al. 2006; Klein et al. 2002).

When investigating the effect of the neurosurgical treatment, as a general observation the surgical resection/reduction of tumour mass, when it is adequately performed with the aid of brain mapping techniques, is beneficial and/or does not further deteriorate the cognitive functioning; however, it can often result in transient focal cognitive deficits. Some studies reported post-operative CD after glioma resection: the percentage of this impairment varied between 24% and 60% with deficit in different domains (Dallabona et al., 2017; Habets et al., 2014; Mandonnet et al., 2015; Noll et al., 2015; Racine et al. 2015; Satoer et al., 2014; Talacchi et al., 2011) and with different post-surgical recovery. The negative effect on patients' cognition seems to be correlated to the size, histology of the tumour, to the volume of the resected area and to the surgical technique used, rather than to the location and/or to a generic mass effect. However, despite the occurrence of post-surgical deficits, due to brain plasticity, cognitive deficits recover (often within 3 months) after a transient post-surgical decline (Duffau et al. 2003; Talacchi et al. 2011) and only a small proportion of patients are not able to return to work or function at their premorbid highest level of functioning. In particular, it is now evident that cognitive decline after the neurosurgical resection is higher in those patients undergoing surgery without cognitive function mapping (Sacko et al. 2011) (see below section 3.4).

As compared with neurosurgical effects, difficult to be measured and quantified, the side-effect of the radiation therapy is better known (Valentine et al. 1998; Correa et al. 2007). Despite some studies (although considering a small sample of twenty patients) reported no evidence of CD after radiotherapy at the 3 and 7 years follow-up (Laack et al. 2005; Brown et al. 2003), it is well

known that cerebral atrophy, microvascular injury and leukoencephalopathy leading to necrosis consequent to radiation therapy have been involved in neuropsychological impairment (Monie et al. 2002; Klein et al. 2003; Sloan et al. 2003; Dietrich et al. 2008). These results were also confirmed by longer follow-up study (Klein et al. 2002 - 1–22 years after diagnosis; mean 6 years; Down et al. 2009 - 6–28 years after diagnosis; mean 12 years): patients with LGG submitted to radiotherapy showed a progressive decline, especially in attentional functioning, compared to non-irradiated patients. The radiotherapy-induced cognitive deficits are associated, in all cases, with radiological abnormalities (i.e. necrosis of white matter or neuroinflammation).

The Neuropsychological side-effects of other treatments such as chemotherapy, the administration of antiepileptic drugs and other clinical factors or complication (infection, endocrine disturbances) also contribute to increasing the risk of CD. Regarding chemotherapy, the negative effects on cognition tend to arise during, or just after, drug administration. Carmustine, methotrexate and cytarabine, has higher CNS neurotoxicity, compared to TZM. In fact, it was reported that progression-free glioblastoma patients undergoing radiotherapy with concomitant and adjuvant TZM treatment do not report cognitive deterioration (Hilverda et al. 2010). Notably, the disclosure of the neurotoxic side-effects exclusively related to chemotherapy is difficult, because often patients, especially with HGG, have already been treated with radiotherapy. In this case, chemotherapy might increase the neurotoxicity due to leakage of the blood-brain barrier caused by radiotherapy (Wen et al. 2003; Correa et al. 2004).

The AED drugs, used to control brain tumour-related epilepsy, also increase the risk of CD in LGG and HGG, although the new generation of AEDs, namely gabapentin, lamotrigine and levetiracetam, have fewer adverse neurocognitive effects (Klein et al. 2003; Taphoorn et al. 2003; Meador et al. 2008).

All the evidences reported above, indicate that the CD in brain tumour patients are mainly influenced by clinical features of the tumour and by adjuvant and antiepileptic treatment. However, it is difficult to disentangle the effects of the individual factors considered in this complex and evolving context, because while the tumour growth may hide the beneficial effects of the treatment, and, simultaneously, the neural reorganization may compensate for the side-effects of the brain tumour, the adjuvant or concomitant treatment and therapy, and co-morbidity with medical or psychological disturbances may induce additional deficits (Duffau et al. 2003).

Given the high incidence of cognitive symptoms in these patients, and the negative effects of these symptoms on the patient's quality of life and general well-being (Heimans et al. 2002), it is clinically relevant to include an extensive neuropsychological assessment at all stages of

treatment/management of the brain tumour. Cognitive data add important information about 1) the clinical situation of the patient (Weitzner et al. 1997), 2) the tumour progression before the emergence of evident signs on magnetic resonance imaging (Armstrong et al. 2003; Meyers et al. 2003), 3) the options regarding the optimal treatment for the individual patient and quality control regarding the appropriateness of medical treatment.

## *3.2 PSYCHOLOGICAL SYMPTOMS IN BRAIN TUMOUR: MOOD DISORDERS*

It has been reported that, the psychological symptoms, such as anxiety and depression, can also negatively influence the patients' cognitive performance (Taphoorn et al. 2003; Cataneda et al. 2008). About half of brain tumour patients show psychiatric symptoms at some time during illness (Pranckeviciene et al. 2015; Bunevicius et al. 2013; Kallio 1993; Sankila et al. 1992) but just a small percentage of patients report these symptoms as the first clinical manifestation of a brain tumour. The main psychiatric symptoms showed during the brain tumour are (Madhusoodanan et al. 2007):

- Anger: showing verbal and/or aggression, being annoyed easily or being impatient;
- Emotional changes: experiencing sudden changes in feelings, often for no apparent reason e.g. crying over nothing or laughing at things that are not funny;
- Apathy: lack of motivation and of interest, diminished goal-directed behaviour or diminished emotions (unchanging affect, or lack of emotional responsivity to positive or negative events);
- Eating disorders: weight loss and decreased appetite;
- Mood disorders (MD) emergence of depression and anxiety symptoms;

Recent studies reported that patients with brain tumour experience significantly higher incidence of MD compared to a control group of post-spinal surgical patients (Pellettier et al. 2002; Jenkins et al. 2016). The association between MD and the diagnosis of cancer might seem obvious, however when compared with control patients with non-CNS cancers, the patients with brain tumour show higher incidence of Cognitive Disfunctions (CD) and MD (Klein et al. 2003; Janda et al. 2006; Goebel et al. 2011), specifically, depression and anxiety. The literature provides confounding evidence reporting, in brain tumour patients, the prevalence of preoperative and postoperative MD ranging from 5% to 89% in different studies (Litofsky et al 2004; Maino et al 2011). Estimates of the prevalence of depression vary greatly, ranging from 2.8% to 95% (Fox et al.2007, Palese et al. 2012) while the prevalence of anxiety disorders ranges from 13% to 60% (Skarstein et al. 2000;

Staci et al. 2008). The high heterogeneity regarding the prevalence of estimated psychological symptoms in brain tumour might be explained by biases in the psychological assessment, by the lack of prospective studies and by the small sample size of patients studied. Despite the possible criticism, there is consensus on the significant occurrence of anxiety and depression in brain tumour patients both in the pre- and post-treatment period, but the cause is still a matter fo debate.

The brain tumour while impacting directly on the nervous system by inducing the dysregulation of specific brain areas and of the hypothalamic-pituitary-adrenal axis (in turn affecting also the immune system, Spiegel 1996, Horrobin & Bennett 1999) simultaneously triggers an individual psychological reaction (Weitzner 1999). This is due to the fact that patients have to cope with a life-threatening disease with an unpredictable behaviour (Barr 2003) (as well as patients affected by non-CNS cancer) but contextually also with cognitive and neurological inabilities. Coherently the higher incidence of MD in brain tumour patients compared to patients affected by other cancers should not be interpreted as the psychological reaction to cancer itself, but some additional biological factors specifically related to this disease must be considered in the pathogenesis of MD. MD may indeed result from situational fear related to diagnosis and prognosis, but also may be directly related to the effects of the tumour. The location, the speed and the type of tumour (HGG vs LGG) are the most important factors for the development of psychological and personality changes (Jenkins et al.2014; 2016), however, in this respect there are contradicting results in different studies: a higher incidence of depression is reported in HGG patients compared to LGG patients (Anderson et al. 1999), but also the opposite has been observed (Pringle et al. 1999). Interestingly, while according to Irle and colleagues (1994) and to others (Armstrong et al. 2002; Pellettier et al. 2002; Mainio et al. 2003; Gathinji et al. 2009) the severity of the tumour (meningiomas vs LGG vs HGG) does not influence the mood states, the laterality of the tumour seems correlate with MD. Patients with the right hemisphere affected by the tumour, waiting for treatment, show higher levels of anxiety compared to those with the tumour in the left hemisphere, while the latter show higher level of depression with respect to the former (Irle et al. 1994; Jenkins et al. 2016). Despite the increasing scientific interest in this issue, at present, no strong association between MD and clinical variables, i.e. tumour location, histology, and extension of resection (EOR), has been demonstrated. MD are probably most likely to be the result of several factors including organic changes, which might be due to the pathological processes of the tumour itself (edema, raised intracranial pressure, or focal destruction or dysfunction of brain regions), but also to treatment effects (surgery, radiation neurotoxicity, chemotherapy induced toxicity, side-effects from anti-convulsant drugs and high-dose corticosteroids or to the consequent cognitive dysfunction, Jenkins et al. 2016).

Notably, many studies focused the interest on the relationship between MD and CD in brain tumour patients but at present no univocal results were provided due to the heterogeneity of methods and of patients samples compared to healthy subjects and other cancer populations (Castaneda et al. 2008; Skali et al. 2011). However, despite the possible biases, it emerges a clear role of the CD in MD (especially depression) (Taphoorn et al. 1992; Cull et al. 1996).

The extensive analysis of the available literature on this very complex issue leads to the conclusion that brain tumour patients have a higher risk to develop MD compared to patientsa affected by other cancers, but the real incidence of MD in the brain tumour population and the pathogenesis (tumour itself, CD, treatments, psychological reaction to stress induced by treatment) of MD in this brain tumour population is still debated. This issue is of crucial importance because MD in brain tumour patients affect the prognosis and the overall health and quality of life (QoL), thus they must not be neglected or considered of less importance with respect to primary treatment. As a matter of fact MD, and specifically depression in brain tumour patients clearly correlate, irrespectively to the histopathological features of the tumour, with poor health-related quality of life (HRQoL), elevated risk of suicide, more medical complications and poor survival (Pellettier et al. 2002; Litofsky et al. 2004; Mainio et al. 2005; Leistner et al. 2015; Hickmann et al. 2016). Accordingly, depression appears to be significantly related to survival time in brain tumour patients: LGG patients with depression had significantly shorter median survival times after surgery compared with LGG patients, same grade, without depression. Moreoevr this difference did not emerge between depressed versus non-depressed patients with either benign tumours or HGG (Litofsky et al 2004; Mainio et al. 2005).

### *3.3 QUALITY OF LIFE*

For a long time, the main and almost unique aim of the treatment of the brain tumour (including surgery, radiotherapy and chemotherapy) was the prolongation of survival or the progression-free survival. However, there is wide consensus that in patients with incurable diseases, such as a brain tumour, therapy should not just focus on prolonging survival, but should also aim at providing the best QoL during the entire disease course. Attention is growing from the healthcare world on QoL, in that it is vital to point to the centrality of the patient when taking decisions concerning health. The patient's point of view, through his/her perceptions, beliefs, emotions, experiences of daily life becomes a new parameter, equally important to medical/clinical indicators,

in the evaluation of the outcome of treatments, or changes in the state of health of general populations or affected by certain chronic diseases as the brain tumour.

The term "quality of life" is generically defined as "*the individual perception of people's positions in life in the context of the culture and value system in which they live and in relation to their goals, expectations and standards*" (World Health Organisation, 1998, p.1570). Two fundamental components in the definition of Quality of Life, specifically related to health (Health Related Quality of Life, HRQoL) are *multidimensionality* and *subjectivity.* The term "*multidimensionality*" refers to the broad range of domains including physical/functional, emotional, social well-being including the symptoms induced by the disease and its treatment (Aaronson et al. 1988). "*Subjectivity*" refers to the fact that HRQoL can only be considered from the patient's perspective. It is important to consider that the HRQoL is influenced not only by objective factors such as actual clinical conditions and, above all, by the unique experience of every patient. The real concept of QoL refers to "*the patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal*" (Cella et al. 1988). It is indeed a subjective evaluation. When the patients are asked to report how do they feel, their response is only partially related to their manifest behaviour, but it is much more related to their subjective perception of illness, perception of treatment, expectations of self, and appraisal of risk/harm. The HRQoL represents the subjective discrepancy between the actual functional level of the patient and the patient's ideal standard, i.e. which would the functional level expected as "ideal" by the patient. Patients who can adjust their expectations during the "threat of the disease" are also able to better adapt to their illness and treatment.

When considering the HRQoL in particular related to brain tumour patients, due to the high symptom burden as the motor and cognitive and neurologic deficits and/or psychologic disorders, affecting their activities of daily living and well-being, a significant impact on the subjective perception of their QoL is expected (Taphoorn et al. 2010). Accordingly, the HGG and many survivors of LGG patients suffer from CD, increased fatigue and depression, assessed both objectively and subjectively, significantly impacting on the subjective HRQoL (Taphoorn et al. 1992; Struik et al 2009). Surprisingly however, despite the higher incidence of deficits in HGG patients compared to LGG patients, the level of HRQoL is superimposable in the two groups (Osoba et al. 2000; Brown et al. 2006), suggesting that the perception of the QoL is not affected by the grade of tumour, as expected. Lower HRQoL in long-term brain tumour survivors might be related to the extent of CD and the severity of epilepsy (Klein et al. 2003). According to the literature, the principal factors affecting the patient's overall QoL include both demographic

characteristics (gender, level of education, work, etc.), clinical features directly related to the tumour (tumour laterality, size, and location) and the treatments (surgery, adjuvants and AED therapy) (Fig. 3)

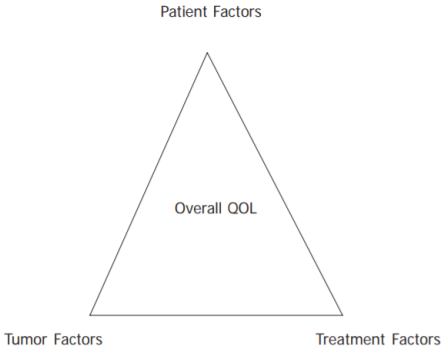


*Fig. 3 Model to evaluate effects of different factors on brain tumour patients' overall quality of life (QOL). From Liu et al. 2009 Neuro-oncology.*

At present, however, the main factors affecting the patient's perception of their own functional, emotional and social well-being remain to be determined possibly also due to the fact that the assessment of QoL is complicated by the relative rarity of this disease compared to other malignancies and by the lack of longitudinal studies.

The disclosure of symptoms that affect QoL is mandatory because the level of HRQoL is a predictor of a survival benefit (Methy et al. 2010) and the improvement of this aspect may in turn increase overall survival (Liu et al. 2009).

The new treatment strategies must be aimed at increasing the duration of survival and, equally important, at avoiding severe side-effects in order to provide the best QoL as long as possible (Efficace et al. 2002).

### *3.4 FUNCTIONAL NEURO-SURGERY: INTRAOPERATIVE BRAIN MAPPING AND THE SYNERGY BETWEEN NEUROPSYCHOLOGY AND NEUROSURGERY*

At present the sole treatment impacting on the natural history of the brain tumour is surgery. Considering the association between MD and CD, the surgical procedure must be aimed at the maximal resection while preserving the functional integrity of the patient. This is actually the aim of functional neuro-surgery, designed to increase the extent of resection (EOR) while simultaneously minimising the risk of damage, preserving neurological and cognitive functions (Duffau et al. 2010). During the past years, considerable evidence indicates a significant increase in survival in patients undergoing a resection above 90% of the total mass and an even greater advantage when

resection exceeded 97% (Lacroix et al. 2001; Sanai et al. 2012; Marko et al. 2014). The increasing importance of the relationship between EOR and increased overall survival (Capelle et al. 2013; Soffietti et al. 2010) encouraged the development of new techniques allowing the neurosurgeons to perform extended resection of tumours also when localized in the so-called *eloquent areas*. The term "eloquent area" refers to specific brain cortical and subcortical structures involved in control cognitive and neurological functions as speech, motor and sensory function, visuospatial abilities etc. Damage to these areas result in major focal deficits. The need to reduce the post-operative deficits to guarantee the highest level of HRQoL possible, favoured the collaboration between neurosurgery and neuropsychology. This synergy is useful when the tumour involves essential eloquent areas included in neural networks underlying neurological and cognitive functions that should be preserved during the resection. Current neuroanatomical knowledge, derived from functional neuroimaging and fiber tractrography helps to localize eloquent areas before surgery, but these informations are not reliable, nor sufficient, to understand anatomic-functional organization of the individual brain of the patient to be treated. The accuracy of exact localization of the functions can be reliably determined only in during surgery performed with intraoperative cortical and subcortical mapping techniques. The Intraoperative Monitoring (IMt) and Brain Mapping techniques (BMt) associated with pre-intra and post-operative neuropsychological assessment are essential in the treatment of brain tumour because they provide the essential information to localize, with accuracy, cognitive and neurological functions allowing to optimize the resection while reducing postoperative deficits (De Benedictis et al. 2010; De Witt Hamer et al. 2012).

Intraoperative Monitoring techniques include electromyography (EMG), electroencephalography (EEG), electrocorticography (ECoG) allowing to monitor the excitability of the cortex and the muscle activation, both voluntary and induced by the Direct current stimulation (DES) delivered during Brain Mapping (BMt). During BMt the direct electrical stimulation (DES) is delivered on of neural structures (cortical and subcortical) surrounding the tumours by using two paradigms: high (HF, 250Hz) or low (LF, 60Hz) frequency DES.

***Electromyography (EMG).*** Continuous recording of EMG during the entire neurosurgical procedure is used to detect: (I) muscle activation due to voluntary activity of the patients; (II) muscle responses (EMG recruitment and motor evoked potentials elicited by LF and HF-DES respectively) to brain mapping stimulation over the motor areas; (III) motor evoked potentials evoked by the MEP monitoring stimulation (see below). The EMG setup in each patient depends on the precise tumour localization, but the standard method is based on positioning up to 24 electrodes, mostly on muscles contralateral (with few electrodes on some ipsilateral muscles) to the

operated hemisphere. The signals are acquired and recorded by means of an electromyographic machine.

***Intraoperative Monitoring of Evoked Motor Potentials (MEP*)** is performed by stimulating the motor cortex by using a train-of-3/5 stimuli at high frequency (230-300Hz) with a strip placed on the primary motor cortex. This technique allows for the monitoring of the integrity of the main essential motor descending pathway through the surgical procedure, i.e. when the surgeon is mapping and resecting the mass. DES stimuli are delivered over the primary motor cortex to induce the activation of the muscles "represented" in the cortical area located under the electrodes. The motor responses elicited in the muscles by DES, called motor evoked potentials (MEPs), are recorded by the EMG electrodes and monitored by the neurophysiological technician. Given that the amplitude and latency of MEPs is related to excitability of both the cortex and spinal cord motoneurons, the occurrence of any event possibly affecting excitability of the cortex (often due to vascular factors not directly related to the site of the procedure), can be real time monitored by inspection of the increase or decrease of MEP amplitude.

***Electroencephalography (EEG)*** is recorded by means of needle electrodes placed in the scalp. This technique allows for the monitoring (and recording) of the activity of brain areas distant from the flap during the procedure and during brain mapping procedures. The main function of EEG monitoring is the early detection of epileptic activity and evaluation of the level of anaesthesia, providing a reliable feedback especially during asleep-awake transitions.

***Electrocorticography (ECoG)*** is recorded with grid electrodes placed directly on the brain cortex to record the activity of the cortex near the surgical site. ECoG, introduced by Wilder Penfield and Herber Jasper, is used to identify the occurrence of after discharges induced by DES. ECoG signals derive from the cortical synaptic activity (excitatory and inhibitory, EPSP and IPSP) and mostly from the synapses of the pyramidal cells on the cortex.

***The Brain Mapping technique*** **(BMt)** is an essential tool for brain tumour surgery to identify eloquent areas of the brain, during the surgical procedure, by means of direct electrical stimulation (DES) of the cortical and subcortical structures surrounding the tumour with a probe during the resection. DES can be used during asleep-asleep anaesthesia or during asleep-awake-asleep anaesthesia. BMt is considered the "gold standard" in neuro-oncologic surgery (De Witt Hammer et al. 2012) because is the most accurate and reliable technique allowing to localize the structures of the brain surrounding the tumour, but still functionally active and thus to be spared from resection. At present BMt allows to identifying, real time, and thus preserving during resection, the cortical and subcortical pathways subserving movement, sensation/perception, language, and other

cognitive functions. In particular, to perform the extended resection while preserving the cognitive functions, it is mandatory to perform intraoperative mapping using BMt in awake patients during the performance of different cognitive tasks (see Fig. 4). The intraoperative mapping is grounded on the main premise that stimulation with DES creates a focal and transitory "disruption" of the activity of the neural elements affected by the current, thus if a cortical or subcortical structure is involved in the neural network controlling the performance of the task, an error or disruption of the performance is expected and the stimulated structure is referred to as "eloquent" and is spared from the resection. BMt is then crucial to distinguish between tissue that needs to be resected (not responsive to DES) and eloquent brain areas that need to be preserved. The intraoperative detection of "positive" responses is used, by the surgeon, to define the functional boundaries of the lesion. Data are recorded and stored in a terminal removed from the operatory field, where they are integrated with neuronavigation data; the collected data can be evaluated offline for research purposes. Using the BMt during the awake phase allows for localisation of cortical and subcortical pathways subserving cognitive and neurological functions such as language, praxis abilities, memory, executive functions motor and visual abilities. To this aim the close cooperation between the neurosurgeon and the neuropsychologist is mandatory.

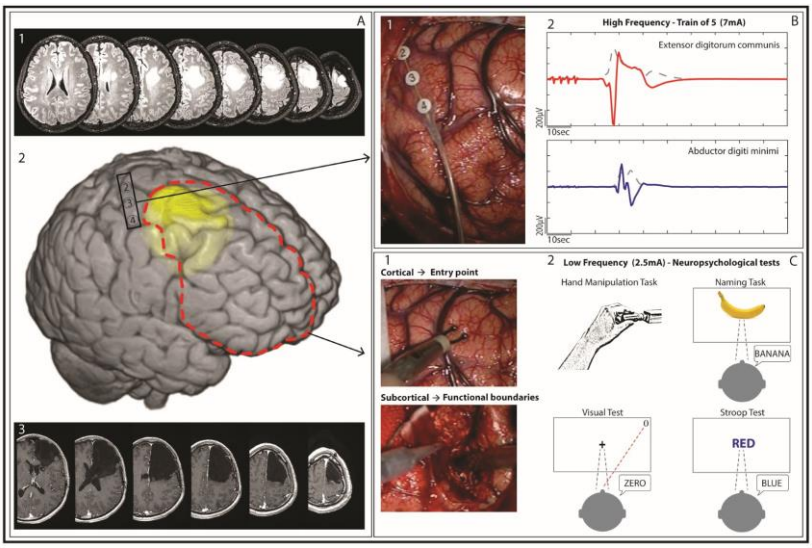


*Fig. 4. Example of rationale underlying Brain Mapping Technique for tumour resection:*
*Panel A - A1: illustrative pre-operative flair indicating location of tumour in the right frontal lobe; A2: 3D reconstruction of patient's brain (yellow shadow indicates tumour position and red dashed line post-operative cavity visible in the axial view in the post-operative T1-MRI (A3).*
*Panel B - B1: localization of the strip recording and stimulating corticospinal related areas during surgery to evoke motor evoked potentials (MEPs, B2) from upper-limb muscles*
*Panel C - C1: Direct electrical stimulation (DES) implemented at cortical (upper) and subcortical (lower) level concomitant to specific intraoperative tools: Hand manipulation task; Naming task; Visual test; Stroop test, (C2).*

Role of the neuropsychologist. Precisely, the neuropsychologist's involvement is aimed at 1) assessment of deficits induced by the tumour itself and its surgical or pharmacological treatment; 2) selection of the correct task or items for the awake brain mapping phase; 3) evaluation of the degree of patient's cooperation; 4) estimation through post-operative assessment of the efficacy of the BMt; 4) assessment of the effects of the disease on the social and familiar context; 5) management of the psychological and social side effect of the disease.

In order to achieve these aims it is necessary: 1) to perform an *extensive and standardized neuropsychological assessment* to evaluate the specific brain functions possibly affected by the lesion and also to highlight residual cognitive strengths that may help the patients to adapt and to cope with their difficulties. This assessment allows for selection of the intraoperative tasks based on the patient's cognitive functioning, on the lesion and on the patient's life features (hobby, work etc.) 2) *to train a patient for the awake phase* in order to minimize negative emotional reactions and to obtain the maximal patient's cooperation. During the "*pre-operative training*" the neuropsychologist recreates, as much as possible, the intraoperative scene to explain to the patient the intraoperative procedure (positioning, possible sensations, how the DES work, etc..) and the importance of his cooperation during the awake procedure. This phase is crucial in that it allows the patient to familiarize with the intraoperative test, and it allows the neuropsychologist to adapt the neuropsychological intra-operative protocol to the pre-operative deficits, removing the items that can cause difficulties to the patient so as not to obtain false negative intraoperative responses; 3) *to assist the patients in the operating theatre and real time evaluate the specific type of symptoms/errors elicited by each stimulation to be reported to the surgeon*, and to help patients to manage the emotional distress assuring the most optimal patient's cooperation.

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# SECTION 2

# RESEARCH PROJECT

# *CHAPTER IV*
# *AIMS OF THE RESEARCH PROJECT*

## *4.1 MAIN AIM OF THE PROJECT*

In the previous chapters an important issue regarding specifically patients with brain tumour has been presented. Brain tumour (BT) increases the risk of incidence of MD, but the absolute incidence of MD in brain tumour patients is not estimated precisely and the pathogenesis of MD in these peculiar population, i.e. whether MD are directly associated with the tumour itself, to cognitive (CD) or neurological deficits induced by the brain tumour or the treatments (surgery and adjuvant therapies) or to the psychological response to the stress secondary to the diagnosis or treatment, is still debated. This issue, for a long time considered a secondary aspect in treatment of brain tumour, is of crucial importance because MD in these patients affects the prognosis and overall HRQoL. MD, and specifically depression in brain tumour patients, are indeed correlated with poor HRQoL and appear to be significantly related to survival time in BT patients, thus must not be neglected.

The research project conducted during the PhD focused specifically on this issue.

Based on the premises presented in the previous chapters, the FIRST AIM of this study was to investigate the prevalence of MD the brain tumour patients and the association of these disorders with the specific clinical and anatomical features of the brain tumour itself and with patients' cognitive outcome. The SECOND AIM was to disclose the influence of MD on HRQoL in patients with brain tumour. Results of this study were used, as main clinical impact, to develop specific "interventions" aimed at improving the HRQoL of the patients with BT, important per se but also in turn related to their survival.

To this end, we performed three subsequent studies:

1. In the first study we analysed a cohort of patients with brain tumour, to evaluate and describe the prevalence of MD and CD in relation to patients' functional state and to the clinical features of the tumour, in order to investigate the relationship with the HRQoL prospectively (Chapter V- Paper in preparation: Leonetti et al. "*Mood disorders in brain tumour patients and effect on Health related quality of life".*)

Based on the results of the first study:

2. In a second study we developed new intra-operative tools in order to reduce the incidence of deficits in Executive Functions, shown to be relevant in development of MD (Chapter VI- Published paper: Puglisi G., Sciortino T., Rossi M., Leonetti A., Fornia L., Conti Nibali M., Casarotti A., Pessina F., Riva M., Cerri G., Bello L. (2018) "*Preserving executive functions in non-dominant frontal lobe glioma surgery: an intraoperative tool"* Journal of Neurosurgery. Vol. 0; No. 0:1-7; 2018)

3. In a parallel third study we developed a new intra-operative tool in order to reduce the incidence of visual deficits shown to be relevant in development of MD (Chapter 7. Paper in preparation Leonetti et al. *"Preserving visual functions during surgery of glioma: a new intraoperative tool"*).

## *4.2 GENERAL MATERIAL AND METHODS COMMON TO ALL STUDIES*

### *4.2.1 PATIENTS*

In a period between 2015 and 2018, consecutive adult patients admitted for brain tumour surgery, at the Department of Oncological Neurosurgery Unit of Humanitas Research Hospital, were included (n=186) and invited to participate in the projects of this thesis. Exclusion criteria, common to all studies, were (1) a history of neurological or severe psychiatric disorder potentially interfering with cognitive functioning and with the reliability of the intraoperative brain mapping, (2) insufficient ability to understand the task or the questionnaire adopted for the studies, due to the inability to speak Italian or due to severe pre-operative neurological deficits. For details related to the specific sample in each study (number of patients included, characteristics of the sample) we refer to the dedicated Chapters.

### *4.2.2 STUDY DESIGN*

All patient gave written informed consent, prior to inclusion in the studies, to the surgical and mapping procedure. All the procedures applied followed the principles outlined in the "World Medical Association Declaration of Helsinki: Research Involving Human Subjects". Patients' consent on the use of data for scientific purposes was collected.

Before the surgery, patients were interviewed for socio-demographic characteristics (age, gender, level of education) and clinical characteristics (history of psychological disorders, use of psychotropic medication). The histology, grading, and molecular profile were determined by pathological examination based on the WHO Classification of Tumours of the Central Nervous System. In this project, we considered patients affected by brain tumour classified into two histological groups: grade I-II gliomas (LGG, low-grade gliomas), grade III-IV gliomas (HGG, high-grade gliomas).

Patients underwent neuroradiological evaluation (see section 4.2.3) and neuropsychological assessment (see section 4.2.4). All patients of each study performed specific tests (see section 4.2.4) 5-7 days before surgery and at precise time pints during the 6 months after surgery (for specific information about individual studies, refer to the relevant chapter).

### *4.2.3 NEURORADIOLOGICAL EVALUATION*

#### *4.2.3.1 PREOPERATIVE NEURORADIOLOGICAL EVALUATION*

During the preoperative period all patients included in this project performed neuroradiological evaluation and specifically performed:

-*Magnetic Resonance Imaging* to identify the tumor location, volume and its relationship with the surrounding structures; MRI was performed on a Philip Intera 3.0T scanner. The MRI protocol included: a) axial three-dimensional fluid-attenuated inversion-recovery (3D-FLAIR) images and b) post-gadolinium three-dimensional T1-weighted fast-field-echo (ffe) images and c) DWI and ADC diffusion weighted images.

-*functional Magnetic Resonance Imaging (fMRI)* For those patients with a tumor location within or in proximity of predictable eloquent areas, fMRI images were acquired with T2-weighted sequences by means of BOLD (blood oxygenation level dependent) technique. This technique allows detection of the cortical areas that have significantly higher BOLD signal levels (as index of metabolic activity of the tissue) during a task performed in the scanner (sensory, motor or cognitive), with respect to other cortical areas, thus identifying the presumed areas involved in task execution and hence that are part of the neural network underlying task execution.

-*Tractography (DTI FT)* This technique enables identification of subcortical pathways and lesion boundaries. The DTI-FT technique allows for indirect reconstruction of the fibers running around and through the tumor, their visualization and the prediction of the subcortical anatomical boundaries of the lesion. MRI and DTI-FT images were loaded into the neuronavigation system for

use during the surgical procedure. DTI-FT and quantitative measurements based on this such as fractional anisotropy are able to quantify tumor infiltration of the corticospinal tract and language fasciculi.

#### *4.2.3.2 POSTOPERATIVE NEURORADIOLOGICAL EVALUATION*

Lesion volume was computed onto FLAIR volumetric sequences with manual segmentation using an iPlan cranial software suite (BrainLab). FLAIR hyperintense signal abnormalities were included in the lesion load for LGGs and were reported in $cm^3$. Patients underwent both an immediate (within 48 h) and a 3-month postoperative MR scan (volumetric FLAIR and post-gadolinium-T1-weighted images) to estimate the extent of resection (EOR). EOR corresponded to the percentage of the volume resected with respect to the pre-operative volume: (preoperative volume-postoperative volume / preoperative volume). We considered total resection a case in which EOR was 100% subtotal when ranged between 90-100%. A supratotal resection was defined post-operatively on MRI as the complete removal of any signal abnormalities with a volume of the postoperative cavity larger (>100%) than the pre-operative tumor volume. Postoperative diffusion-weighted MRI scans were also performed to check for ischemic damage.

### *4.2.4 NEUROPSYCHOLOGICAL ASSESSMENT*

In each patient, an extensive neuropsychological evaluation was performed in order to: 1) detect severe or subtle cognitive deficits; 2) tailor the intraoperative brain mapping to the patient specific features and, postoperatively, to assess the impact of surgery and of adjuvant therapy on the patient's functions, an extensive neuropsychological evaluation was performed. All subjects included in this project were evaluated at four time points: 5-7 days before operation (T1), at 1 month after surgery (T2), at 3 months after surgery (T3) and at 6 months after surgery (T4).
For each time point, all patients were evaluated using standardized tests of the following cognitive domains: 1) language, 2) attention and executive functions, 3) memory, 4) praxis and visuo-constructional abilities. For each domain we used selected tests that we describe below:

1) **Language Tests**:
    - ✓ *Verbal fluency on phonemic and semantic cue (Novelli et al. 1986)*: is a test to measure lexical and semantic access; phonemic fluency places higher demands on frontally-mediated strategic search processes. The patient is asked to say as many

words as possible starting with the letter (phonemic fluency: F, P and L) or belonging to the same semantic categories (semantic fluency: automarkers, fruits and animals) in 1 minute. Letters and the categories are suggested by the examiner.

- ✓ *Object picture naming (Catricalà et al. 2012):* the patient is asked to name 48 different pictures presented comprising living and non-living objects.
- ✓ *Token test (Spinnler et al. 1987)*: this test evaluates patient's comprehension of 36 oral commands divided into 6 groups of growing complexity, that demand the performance of practical tasks using "tokens" of different color and shape.

**2) Attentive and Executive Tests**

- ✓ *Attentive Matrices (Spinnler et al. 1987)*: is a valid instrument to measure selective attention. It includes three matrices of 130 digits, arranged on 13 lines of 10 items each, which are presented in succession to the subjects; the patient is required to check, by ticking with a pencil, the digits to find a target number (from one to four digit) scattered among all the others digits present, which act as distractors.
- ✓ *Trail Making Test - TMT (Giovagnoli et al. 1996)* is considered to be a measure of mental flexibility. The test is given in two parts: Part A requires patient to connect a series of consecutively numbered circles, and thus involves visual scanning, number recognition, numeric sequencing and motor speed, while Part B requires patients to alternate between connecting numbers and letters in numerical and alphabetical order. In both parts, the score is based on the time taken to complete the test, including any error correction time. However, the use of TMT-B minus TMT-A (B–A in seconds) has been recommended as a more sensitive measure of executive control.
- ✓ *Stroop test (Caffarra et al. 2002)* is composed of three sub tasks, in which the patient is instructed to respond as fast and as accurate as he/she can to the relevant stimulus attribute: in the first subtask the subject is asked to read a list of color names ("red", "blue" or "green"); in the second subtask the patients had to name the colored circle (red, blue or green); such two sub-tasks are useful to exclude reading or perceptual difficulties. In the last "conflict" subtask, i.e. the "Color-word Subtask", executive functions aspects are specifically evaluated: patients are presented with a series of color words printed in an incongruent hue ("blue" printed in red hue) and are required to inhibit the automatic tendency to read the written color (blue) in order to name the incongruent color of ink in which the word is written (red).

- ✓ *Colored Raven's progressive matrices (Basso et al. 1996):* is a multiple-choice test. It consists of a series of visual pattern matching and analogy problems pictured in non- representational designs. It requires the patient to conceptualize spatial, design, and numerical relations ranging from the obvious and concrete to very complex and abstract. The patient is presented with a set of 36 incomplete figures and their task is to complete the set by choosing one of the six response alternatives given below the figure.

3) **Memory test**:

- ✓ *Digit Span forward and backward (Monaco et al. 2012):* these tests are reliable and valid measures of short-term and working memory respectively (Strauss et al. 2006). The digit span forward test consists of 16 trials, starting with 2 digits and ending with 9 digits. The digit span backward test consists of 14 trials starting with 2 digits and ending with 8 digits. In the forward version the patient is asked to repeat sequences of numbers in the exact order read out by the examiner, instead in the backward version the patient is asked to repeat sequences of digits backwards. Both tests begin with two to three numbers, increasing until the person commits errors. The "span" is given by the sequence with the highest number of stimuli correctly repeated.
- ✓ *Rey Auditory Verbal Learning Test (RAVLT, Carlesimo et al. 1996):* this is a well-recognized measure of a person's ability to encode, combine, store and recover verbal information in different stages of immediate memory. A 15 noun-word list is read to the patient with a presentation rate of one word per second, specifying that the order is not important; after presentation of the 15 words the patient is requested to recall as many words as possible. The procedure is repeated 5 times, and after each trial the number of words recalled is recorded. This part of the test is the immediate RAVLT. Delayed RAVLT is measured asking the patient to recall the 15 noun-word list 15 minutes after the immediate recall. In the meantime, no verbal tests are administered to the patient, not to create any interference in the delayed score.
- ✓ *Rey-Osterrieth Complex Figure test recall (ROCF Cafarra et al. 2002):* this is a widely used figural copy and recall task, adopted to test both visuo-spatial functions and long-term visual memory. The visual memory component of the ROCF involves participants redrawing a figure from memory in an allocated time after the copy trial

(10 minutes after copy). The drawings are scored according to an assessment of 18 particular characteristics of the figure.

**4) Visual perception and constructional praxis evaluation**

- ✓ *Rey-Osterrieth Complex Figure test copy (Cafarra et al. 2002)*: the visuo-spatial abilities of the patient are evaluated with the drawn copy of a complex figure presented to the patient. This test allows for the assessment of alteration of visuo-spatial integration (evaluation of observed object orientation and position in space) and of the motor program necessary to produce a spatial construction (from planning to execution).
- ✓ *Ideomotor apraxia (De Renzi et al.1980)*: is administered to assess the ability to carry out movements on imitation. The test is composed of 24 items in which finger movements and whole arm movements were required, half of which were meaningful and the other half meaningless.

**5) Mood Disorders and Quality of life**

- ✓ "*Hospital Anxiety and Depression Scale" (HADS, Zigmond & Snaith 1983).* The HADS consist of 14 items assessing anxiety and depressive symptoms (For example, anxiety items "*I feel tense or 'wound up*'; get sudden feelings of panic; depression items: "*I still enjoy the things I used to enjoy*", "*I have lost interest in my appearance*"). Patients were asked to circle the sentence that best represents their feeling at the time of evaluation. Each item is scored from 0 to 3 (total 21 points). Scores for each subscale (anxiety and depression) ranged from 0 to 21. Patients were classified based on their individual overall score. A cut-off total score of > 7 identified moderate symptoms of anxiety and the score of > 10 identified moderate symptoms of depression.
- ✓ "*Health Related Quality of Life was evaluated by using the self-report questionnaire "Short Form 36 items Health survey (SF36)".* This questionnaire includes eight multiple-item subscales, four scales evaluate physical health (subscales physical function, role limitations due to physical problems, pain and general health) and four scales evaluate Mental Health (vitality, social functioning, perception role limitations due to emotional problems, mental health). Total score on each SF-36 subscale ranges between 0 and 100. Higher score indicates better Health related quality of Life (HRQoL).

All the tests used for the evaluation have proven to be sensitive enough to detect severe but also very mild deficits (Papagno et al. 2012)

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# *RESULTS SECTION*

**STUDY 1:**

***"THE EFFECTS OF COGNITIVE AND MOOD DISORDERS ON HEALTH-RELATED QUALITY OF LIFE IN ADULTS WITH BRAIN TUMOR"***

**STUDY 2:**

***"PRESERVING EXECUTIVE FUNCTIONS DURING SURGERY OF GLIOMA: A NEW INTRAOPERATIVE TOOL".***

**STUDY 3:**

***"PRESERVING VISUAL FUNCTIONS DURING SURGERY OF GLIOMA: A NEW INTRAOPERATIVE TOOL"***

# *CHAPTER V*
# *STUDY 1 "THE EFFECTS OF COGNITIVE AND MOOD DISORDERS ON QUALITY OF LIFE IN ADULTS WITH BRAIN TUMOUR"*

## *5.1 INTRODUCTION*

Primary Brain Tumour, mainly gliomas, is an infiltrating chronic disease harbouring within the central nervous system (CNS). Brain tumour prognosis is very poor, leading to death in a significant percentage of cases, although the prognosis depends on the type of tumour, the worse being the malignant gliomas with median survival ranging from 12–15 months for glioblastoma multiform (GBM) and from 2–5 years for anaplastic gliomas (for details see Chapter II). As a peculiar feature, during its growth within the CNS, the tumour induces, depending on the localization, motor, cognitive, behavioural and psychiatric manifestations (for details see chapter 3). At present, the extent of resection (EOR) is reported as the main factor significantly affecting the natural history of the disease and, ultimately, the prognosis.

In this, light, considering the poor prognosis of many brain tumour, the optimization of the surgical procedure, with the aid of the brain mapping techniques (BMt, for details see Chapter III) seems mandatory, given that it allows to performing "supratotal resections" (i.e. an extended removal of the tumour's borders beyond the MRI-defined abnormalities), while preserving the brain areas and systems of fibers essentials for the main neural and cognitive functions. This double goal is aimed at increasing the patients' survival or free progression survival and at assuring to the patients, as much as possible, the best quality of life, strictly depending on their ability to perform daily and social activities.

As reported in the Chapter III, often, in brain tumour patients aside to the impairment of the principal cognitive functions, there is a high incidence of is associated with mood disorders (MD). The higher incidence of MD in patients affected by brain tumour when compared to patients affected by cancer not related to CNS, points to the conclusion that the MD in brain tumour patients cannot be interpreted as the sole psychological reaction to cancer itself, but may be significantly related to some additional distinguishing biological features of this disease. However, at present, no significant association between MD and clinical variables, including tumour location, histology, and EOR, has been reported.

A specific factor associated to brain tumour is the occurrence of cognitive dysfunctions (CD) and neural deficits, due to the effect of the lesion itself or being the consequence of treatment (see Chapter III). With respect to the non-CNS cancers, patients with brain tumour show higher incidence of both CD and MD (Klein et al. 2003; Janda et al. 2006; Goebel et al. 2011). These observations rise the question of whether, in brain tumour patients, MD might be directly associated to the CD or the neurological deficits induced by the tumour itself or resulting from the treatments (surgery and adjuvant therapies). As discussed in the previous chapter, the disclosure of the main factors associated to MD in this patients is of great clinical relevance in that, on one side MD may negatively impact on crucial aspects of care such as the compliance of treatments and eventually on the survival and, on the other side, they cause a decline in functional independence more than the decline due to physical disability with a significant impact on Health Related Quality of Life (HRQoL). The improvement in HRQoL is associated with longer survival especially of HGG patients, while poor HRQoL is associated with shorter expectance of life (Litofsky et al 2004, Maino et al. 2006). Based on this evidence, the evaluation of MD and HRQoL, the investigation of their main determinants and of the interplay between both, is not only mandatory to allow an unbiased evaluation of patient's cancer care outcomes but might also be considered as early independent predictors of survival (Mauer 2007). In the last decade a significant effort has been devoted to the investigation of HRQoL as an important end point in brain cancer studies, focusing on the negative influence of several clinical factors such as CD and MD on HRQoL that, however, still needs to be better defined.

The clinical experience matured by the neurosurgical team in the past years, with a high number of patients with brain tumours (about 400/year), seem to confirm that in their path from diagnosis to treatment (surgery and adjuvant therapies as chemo or radiotherapy), patients face many stressors, among which the CD, reasonably leading in the development/emergence of MD and specifically anxious or depressive responses. However, at present the critical issue of whether the clinical features related to the tumour (its location, histology etc.) or rather the psychological response to the stressors secondary to the diagnosis or treatment (Madhusoodanan et al. 2015) must to be considered predictors for emergence of MD in brain tumour patients, is still unsolved.

Aim of the study was thus to investigate the prevalence and the association of MD with both the specific clinical and anatomical features related to the tumour itself and with the patients' cognitive outcome, aimed at disclosing the influence of CD on the emergence of MD and, consequently the effect of the latter on HRQoL. Results were analysed to identify, during pre-surgery period, the

clinical predictors of MD to develop specific interventions to improve the prognosis and the QoL of patients.

## *5.2 MATERIALS AND METHODS*

### *5.2.1. PARTICIPANTS /POPULATION*

For this fist study a prospective, longitudinal, single-center study was performed. Between March 2016 to June 2018, 116 patients among the patients submitted to surgical resection of intracranial brain tumour meeting the inclusion criteria were enrolled. Patients were recruited in the Department of Neurosurgery Oncology (Humanitas Research Hospital), directed by Prof. Lorenzo Bello. All patients included in this study had to fulfil the following inclusion criteria: age ≥ 16 years, sufficient comprehension abilities, absence of major psychiatric impairments (see also general methods chapter 3).

For each patient, the clinical records were reviewed and the relevant data relative to the tumour (type, grade, location, relapse), the treatments post-surgery (chemotherapy and radiotherapy) and on the demographics characteristics (age, gender and level of education) recorded (see Table 1 – for the demographic and clinical characteristics of participants).

### *5.2.2 EVALUATION TOOLS*

All patients underwent a detailed psychological and cognitive assessment. Two measurements have been selected for the studies to measure MD and HRQoL of the patients: HADS and SF36 (for details see 4.2.4 paragraph of Chapter IV).

All selected assessments are very commonly used and thoroughly validated in brain cancer population (Papagno et al 2012; Bunevicius et al. 2017).

All patients were tested immediately before surgery (T0), at 1 month after surgery (T1), at 3 months after surgery (T2) and at 6 months after surgery (T3).

### *5.2.3 STATISTICAL ANALYSIS*

All statistical analyses were performed using IBM SPSS Statistics Software.

For each patient the occurrence or absence of cognitive (CD) or psychological deficit (MD) and the score of SF36* was evaluated at T0 (before surgery), T1 (1month post-surgery), T2 (3 months post-

surgery) and T3 (6 months post-surgery). At each time point, a chi-square and Fisher's exact tests were used (p<. 0.05 was considered statistically significant) to assess the association between demographic and clinical factors (age, gender, education, histology, tumour grade, tumour site and cognitive functions) and the occurrence of a reactive mood disorder, MD.

Regarding the Health-Related Quality of Life (HRQoL) the difference in mean score of SF36 between different characteristics of the tumours and different functional outcome (CD and MD) were evaluated using the One-way ANOVA. For each analyses the level of significance was set to p<. 0.05.

## *5.3 RESULTS*

### *5.3.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS*

Patients (n=116, mean age 48 ± 13 years; range 16-77 years) were prevalently males (89%; n 77), with had high school diploma (13 years; 66%; n 58). The majority of the patients recruited was affected by a High Grade tumour (WHO grade III-IV 56,9%). Tumours were predominantly located in the left hemisphere (56,9%;) involving the frontal lobe in the majority of the participants (51%). All clinical characteristics of the participants are summarized in Table 1.

*Table 1. The frequency of the clinical characteristics of participants.*

| Variables | % | n |
|---|---|---|
| **HYSTOLOGY OF THE BRAIN CANCER** | | |
| *Glioblastoma* | 41,4 | 37 |
| *Oligodendroglioma* | 26,9 | 24 |
| *Astrocitoma* | 16,8 | 15 |
| *Anaplastic Astrocitoma* | 15,7 | 14 |
| *Other brain cancer* | 20,2 | 26 |
| **WHO GRADE** | | |
| *Low Grade (I – II)* | 37,9 | 44 |
| *High Grade (III – IV)* | 56,9 | 66 |
| **HEMISPHERIC LATERALITY** | | |
| *Right* | 43,1; | 50 |
| *Left* | 56,9; | 66 |
| **TUMOR LOCATION** | | |
| *Frontal* | 51,0 | 60 |
| *Temporal* | 30,2 | 35 |
| *Parietal* | 16,4 | 19 |
| *Cerebellum* | 1,7 | 2 |
| **RELAPSE** | | |
| *Yes* | 16,4 | 19 |
| *No* | 81,9 | 95 |
| **ADJUVANT THERAPY (started 1 month after surgery)** | | |
| *Chemotherapy* | 56,0 | 65 |
| *Radiotherapy* | 55,2 | 64 |

### *5.3.2 Cognitive (CD), Neurological and Mood disorder (MD) and Related Health Quality of Life (HRQoL) in brain cancer patients*

#### *5.3.2.1 Neuropsychological Assessment*

***Incidence of cognitive deficits (CD) in brain tumour patients.*** Results of neuropsychological assessment showed that over time during the treatment, only 1/3 of the total patients was affected by a CD (see Table 2); notably after surgery we found an increase of neuropsychological deficit <15% compared to the pre-surgical evaluation, highlighting that the impact of surgery on incidence of CD was very low. Interestingly, the distribution of the prevalence of the different CD is not homogeneous: the prevalence of language, attentive and executive deficit is higher, over time, with respect to apraxia, motor and visual deficit. Differently, the incidence of memory deficit does not increase over the time of treatment.

*Table 2. Incidence of cognitive and neurological deficits*

| Cognitive deficit | Pre Surgery % | 1 Month after treatments % | 3 Month after treatments % | 6 Month after treatemnts % |
|---|---|---|---|---|
| **Language** | 20 | 29,5 | 32,8 | 32,4 |
| **Attentive and Executive** | 18,4 | 25,8 | 22,4 | 27,3 |
| **Memory** | 29,9 | 31,8 | 30,8 | 23,3 |
| **Apraxia** | 0 | 2,5 | 3,3 | 3,8 |
| **Motor** | 2,8 | 19 | 12,4 | - |
| **Visual** | 3,8 | 17,9 | - | - |

#### *5.3.2.2 Psychological Assessment- HADS questionnaire*

***Incidence of mood disorders (MD) in brain tumour patients.*** Overall results show that the incidence of MD increases after surgical and adjuvant treatment and, particularly **depression**, increase at 3 and 6 months after treatments. Notably, when requested, chemotherapy and radiotherapy start at about 1 month after surgery.

Regarding the incidence of **anxiety**, this disorder emerges in 40% of the patient with brain tumour before treatment (see Table 3a for the prevalence data) and, differently from depression, its does not increase over time.

*Table 3a. Incidence of Mood Disorder*

| | Pre Surgery % | 1 Month after treatment % | 3 Month after treatment % | 6 Month after treatment% |
|---|---|---|---|---|
| **Mood Disorder** | 39,5 | 44 | 52 | 38,5 |
| **Anxiety** | 40 | 39 | 43 | 34 |
| **Depression** | 10,7 | 23,9 | 39,2 | 40 |

***Correlation between MD and clinical/demographical parameters***

In order to verify the association between mood disorders and clinical or demographical characteristics of the population, for each time window considered ($T_0$…$T_4$) the incidence of both anxiety and depression were statistically verified in association with demographic and clinical characteristics of the tumour.

The results confirmed the preliminary data collected during the first year of the project, showing that before treatment ($T_0$) there are no significant associations between anxiety or depression and all demographic characteristics (gender, education and age) or clinical characteristics of the tumour (malignancy, location, adjuvant therapy). Interestingly, the present analysis confirmed the significant association between depression and "hemispheric laterality" at 1 and 3 months after surgery ($T_1$ and $T_3$): at 1 month after surgery 35% of the patients with left hemispheric tumour, developed depression compared to the 9.7% of the patients with the right hemispheric tumour (p value < 0.023), this value increasing to 51,7% at 3 months after surgery, compared to the 22,7% of incidence at the same time window in patients with the right hemispheric tumours (p value < 0,046). The association demonstrated between depression and hemispheric localization of the tumour, at 1 and 3 months after surgery, might lead to the conclusion that is the hemisphere affected that –plays a direct effect on the psychological condition of the subjects.

However, given the absence of a correlation between MD and clinical features of the tumour *per se*, this association might be explained by the fact that the patients with tumours affecting the left hemisphere, hosting the dominant network subserving complex cognitive functions, show a higher incidence of cognitive post-surgical deficits (CD) which are more difficult to recover as shown in the Table 3 (incidence of cognitive and neurological deficits). In this light it could be hypothesized that MD in brain tumours are primarily a psychologically mediated response to disability, thus including the loss of cognitive efficiency.

*Table 3b Mean(M) and standard deviation (SD) of HADS for each demographic and clinical characteristics.*

| Demographic and Clinical Characteristics | HADS_A Pre M –(SD) | HADS_A 1 Month M –(SD) | HADS_A 3 Months M –(SD) | HADS_A 6 Months M –(SD) | HADS_D Pre M –(SD) | HADS_D 1 Month M –(SD) | HADS_D 3 Months M –(SD) | HADS_D 6 Months M –(SD) |
|---|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | | |
| *Male* | 6,69 (3,79) | 6,45 (4,06) | 6,56 (3,97) | 5,25 (3,53) | 3,67 (3,40) | 5,73 (4,09) | 6,17 (3,77) | 6,88 (4,67) |
| *Female* | 7,14 (3,85) | 7,19 (4,66 | 5,82 (5,07) | 6,23 (4,39) | 3,90 (3,17) | 5,44 (3,54) | 5,81 (3,91) | 5,12 (4,32) |
| **Lobe affected** | | | | | | | | |
| *Frontal* | 6,38 (3,97) | 5,91 (4,77) | 7,08 (4,99) | 5,39 (3,73) | 3,38 (3,51) | 5,74 (3,69) | 6,64 (3,68) | 6,33 (5,03) |
| *Temporal* | 6,27 (2,91) | 6,26 (3,84) | 6,13 (3,50) | 6,57 (4,04) | 4,41 (3,19) | 5,26 (4,24) | 7,60 (4,00) | 8,14 (4,30) |
| *Parietal* | 5,75 (3,79) | 5,47 (4,14) | 6,56 (3,40) | 6,50 (5,25) | 3,83 (3,07) | 5,87 (4,14) | 6,33 (4,00) | 7,33 (4,99) |
| *Cerebellum* | 3;00 (-) | 4,50 (0,71) | 3,5 (2,12) | 4,59 (-) | 2,00 (-) | 5,00 (4,24) | 4,5 (2,12) | 5,00 (-) |
| **Laterality** | | | | | | | | |
| *Left* | 5,73 (4,15) | 6,80 (4,27) | 6,77 (4,03) | 6,22 (3,81) | 3,70 (3,93) | 6,78 (4,15) | 7,83 (3,94) | 7,88 (4,49) |
| *Right* | 6,45 (3,34) | 5,23 (4,15) | 5,68 (4,71) | 6,25 (5,80) | 3,77 (3,27) | 3,13 (2,90) | 4,31 (3,24) | 6,25 (6,15) |
| **Grade** | | | | | | | | |
| *Low* | 6,47 (4,06) | 5,73 (4,67) | 5,67 (4,15) | 5,82 (3,25) | 3,69 (3,24) | 5,15 (3,18) | 7,55 (3,71) | 5,36 (4,17) |
| *High* | 5,76 (3,73) | 6,44 (4,26) | 6,90 (4,52) | 7,35 (5,09) | 3,78 (3,46) | 5,95 (4,28) | 6,90 (3,83) | 7,38 (4,10) |
| **Relapse** | | | | | | | | |
| *Yes* | 4,58 (4,05) | 5,63 (4,08) | 4,80 (3,89) | 5,00 (2,41) | 3,25 (3,80) | 6,00 (4,17) | 5,00 (3,53) | 3,50 (2,71) |
| *No* | 5,31 (3,78) | 6,17 (4,33) | 6,58 (4,31) | 6,50 (4,46) | 4,08 (3,35) | 5,57 (3,86) | 6,93 (3,86) | 5.86 (3,90) |
| **Adjuvat Therapy** | | | | | | | | |
| *Yes* | 6,62 (3,82) | 6,77 (4,19) | 6,43 (4,09) | 7,07 (5,10) | 4,10 (3,48) | 6,11 (4,21) | 7,58 (3,66) | 8,92 (5,21) |
| *No* | 5,78 (3,80) | 4,96 (4,09) | 7,00 (4,42) | 5,25 (3,33) | 3,04 (2,88) | 4,88 (4,20) | 5,64 (3,85) | 6,66 (4,37) |

### *Psychological Disorder (MD) and Cognitive Deficits (CD)*

To clarify whether MD are actually correlated to disability, the association between MD, CD and functional outcome was investigated. To this aim we divided the population of patients in different groups based on the recovery of general and specific deficits: General recovery vs No-General recovery; Language, or Attention, or Memory or Apraxia or Motor or Visual Recovery groups vs Language, or Attention, or Memory or Apraxia or Motor or Visual No-Recovery groups.

The analyses failed to show a statistical association between the incidence of MD and specific CD or neurological deficit – language, memory, attentive/executive deficit, apraxia, motor and visual disorder.

These results, together with the clinical observation of patients, suggested that the increasing prevalence of MD after treatments might be caused by the lack recovering of the CD or neurological deficits rather than by the occurrence of the deficits (either specific or general) *per se*.

When considering the No-Recovery groups it emerged indeed that:

Evaluation at **$T_1$ (1 month after treatment).** Patients not recovering from language, motor and visual deficit showed an incidence of MD higher than patients recovering from the same deficits. Specifically:

-42,1% of the patients not recovering the language ability showed MD and specifically depression (M 7,53 – SD 4,70), compared to the 18% of the patients who recovered (M 5,32 – SD 3,51) (*p value < 0,05*);

-70% of the patient affected by the motor deficit (M 8,14- SD 3,14) showed MD compared to the 39% of the patient who recovered (M 5,15- SD 2,14) (*p value < 0,05*);

-66,7% and the 50% of the patients affected by visual deficits showed MD and respectively anxiety (M 8,08- SD 4,14) and depression (M 8,67 – SD 4,1) compared to the 30,9% and 16,4% of patients who recovered (Anxiety: M 5,29 – SD 3,07; Depression M 4,92 – SD 3,55) (p value <0,04; <0,02)

Evaluation at **$T_2$ (3 month after treatment).** At 3 months the results confirmed the percentage of the patients not recovering from language (No Lang, Recovery: M 8.84 -SD 4,20 vs Lang. recovery: M 5,36- SD 3,68) and visual deficits (No Visual, Recovery: M 8.22 -SD 2,24 vs Visual. recovery: M 5,05- SD 3,62) and show also that 81,8 % of the patients not recovering the attentive and executive functions showed a mood disorder (M 8.94 – SD 3.03) compared to the 46,3% of the patients who recovered (M 5,27 – SD 3,88) from the same deficits (p value <0,046). At 3 months no difference between motor recovery group and no motor recovery group was found because, thanks to the BMt used in our group, the occurrence of permanent motor deficit is very low and the most of patients recover from motor impairment within 2 months.

Evaluation at **$T_3$ (6 month after treatment).** The results confirmed the results described for the evaluation at 3 months. Moreover, at 6 months after treatment we found that patients who did not recover the *general cognitive* or neurological functions showed a MD. Specifically:

-52,9% of patients not recovering showed anxiety (M 8,30 – SD 4,83) compared to the 11,1% of patients who recovered (M 4,22 – SD 2,58) (p value <0,045);

-56,2 % of the patients not recovering showed depression (M 9,07 – SD 5,01) compared to the 11,1% of patients who recovered (M 4,33 – SD 3,55) (p value <0,040).

Overall the analysis of the results showed that the persistence of language, attentive/executive, visual and motor deficit significantly impacts on the psychological status of the patients. However, while the CD *per se* is not predictive of the emergence of MD, it is the lack of recovery that seems to predict the occurrence of anxiety and depression. In this light it could be suggested that, it is not the CD or neurological loss that plays a significant role in the emergence of MD, but the expectance of patients on their recovery. Irrespective of the nature or gravity of deficits, if the patient did not improve over time, he/she was more likely to develop a reactive MD.

#### *5.3.2.3 Health Related Quality of Life - SF 36 questionnaire*

***Scores in the HRQoL in brain tumour patients.*** The Health Related Quality of Life (HRQoL) of brain tumour patients was measured using the SF36 questionnaire. The analyses of the mean score of the subscale showed that **before treatment** ($T_0$) the lowest SF-36 scores were

observed for the subscale "*Role limitation due to physical problem*" while the highest scores were observed for the "*Physical Functioning*" and "*Pain*" subscales (Table 4 shows the mean score on the SF36 subscales). **After treatment (1, 3 and 6 months)**, we observed score below the average in the 3 subscale "*Role of limitation due to physical and mental problem*" and in the "*Social functioning*" subscale.

*Table 4. SF 36 Questionnaire score*

| | | Before Surgery | 1 Month After surgery | 3 Month after surgery | 6 Month after surgery |
|---|---|---|---|---|---|
| | M (SD) Health Population | Mean Score (% 0-100) | | | |
| **Physical Health** | | | | | |
| **Physical Functioning** | *84,2 (23,3)* | 87 | 73 | 74 | 69 |
| **Role limitation due to physical problem** | 81 (34) | *48* | *21* | *32* | *52* |
| **Pain** | 75,2 (20) | 74 | 67 | 71 | 73 |
| **General Health perception** | 72,0 (20,3) | 65 | 57 | 54 | 56 |
| **Mental Health** | | | | | |
| **Vitality** | 60,9 (21) | 58 | 54 | 51 | 51 |
| **Social Functioning** | 83,3 (22,7) | 67 | *49* | *55* | *63* |
| **Role limitation due to emotional problem** | 81,3 (33) | 56 | *34* | *49* | *43* |
| **Mental Health perception** | 74,7 (18) | 65 | 61 | 59 | 60 |

### *5.3.2.4 The effect of Cognitive and Mood Disorders on the HRQoL*

***The impact of CD and MD on the Health Related Quality of Life of BT patients*** was estimated by comparing the mean score of each subscale of SF36 with all the clinical and demographics characteristics of the population and with all the cognitive and psychological symptoms by using a One Way ANOVA test.

The results (see Table 4) showed that:

**Evaluation at $T_0$**. Before surgery patients with Memory and MD showed the lowest scores in the principal subscale of Mental Health, while the pre-surgical motor deficits seem to influence only a single aspect of the HRQoL and specifically the Physical Function.

**Evaluation at $T_1$**. One month after surgery the language, motor and mood disorders impact on other aspect of the HRQoL including General Health and all the subscale of Mental Health, not affected in the presurgical period by the same deficits.

**Evaluation at $T_3$ and $T_6$.** At 3 and 6 months after treatment, aside to the occurrence of language and memory disability and mood disorders, emerged that the lack of recovery of the language, memory, attentive/executive and visual deficit significantly impacts on the main subscale of the

Sf36. Specifically, the MD and the lack of recovery of visual deficit seem to be the two main factors influencing the majority of the Mental Health subscale.

*Table 5. One-Way ANOVA result of SF36 Questionnaire*

| **Functions** | **Sf 36 Sub scales** | | | |
|---|---|---|---|---|
| **BEFORE SURGERY** | | Mean score % | Mean score % | |
| **Memory** | Pain | 64,5 | 80,5 | 0,029 |
| | Vitality | 49,4 | 62,9 | 0,049 |
| | Mental Health | 56,2 | 69,2 | 0,042 |
| **Motor** | Physical Functioning | 74 | 84 | 0,019 |
| **Mood Disorders** | Pain | 64,3 | 80,1 | 0,042 |
| **Mood Disorder** | General Health | 53,5 | 70,1 | 0,002 |
| | Vitality | 48,3 | 62,8 | 0,019 |
| | Social Functioning | 48,8 | 77,6 | 0,000 |
| | Mental Health | 52,4 | 72,2 | 0,001 |
| | | | | |
| **1 MONTH AFTER SURGERY** | | Mean score % | Mean score % | |
| **Language** | General Health | 50,9 | 67,3 | 0,046 |
| **Motor** | Physical Functiong | 49,4 | 76,4 | 0,000 |
| | Social Functioning | 28,1 | 50,5 | 0,018 |
| **Mood Disorders** | Physical Functiong | 64,8 | 78,2 | 0,019 |
| | Role limitation physical problems | 6,58 | 30,0 | 0,021 |
| | General Health | 44,1 | 63,5 | 0,007 |
| | Vitality | 42,4 | 58,6 | 0,016 |
| | Social Functioning | 36,9 | 53,5 | 0,012 |
| | Mental Health | 46,3 | 69,1 | 0,001 |
| **3 MONTH AFTER SURGERY** | | Mean score % | Mean score % | |
| **Memory** | Pain | 43,7 | 78,5 | 0,004 |
| | Viatlity | 35,0 | 54,6 | 0,050 |
| **Language** | General Health | | | |
| **Recovery Language** | Pain | 44,5 | 76,7 | 0,004 |
| | General Health | 50,0 | 70,3 | 0,036 |
| **Recovery Attention/executive f** | Vitality | 31,9 | 53,3 | 0,025 |
| | Mental Health | 36,0 | 62,5 | 0,006 |
| **Recovery Visual functions** | General health | 35,3 | 58,5 | 0,016 |
| | Vitality | 34,5 | 54,5 | 0,021 |
| | Social Functioning | 38,8 | 61,2 | 0,008 |
| | Mental Health | 41,2 | 62,2 | 0,021 |
| **Mood Disorders** | General Health | 40,1 | 66,5 | 0,001 |
| | Vitality | 37 | 62,1 | 0,000 |
| | Social Functioning | 39,8 | 70,8 | 0,000 |
| | Role limitation emotional problems | 25,4 | 71,4 | 0,000 |
| | Mental Health | 43,6 | 71,4 | 0,000 |
| | | | | |
| **6 MONTH AFTER SURGERY** | | Mean score % | Mean score % | |
| **Memory** | Pain | 46,0 | 78,0 | 0,005 |
| | Viatlity | 35,0 | 54,6 | 0,005 |
| **Language** | General Health | | | |
| **Recovery Language** | Pain | 44,5 | 76,7 | 0,004 |
| | General Health | 50,0 | 70,3 | 0,036 |
| **Recovery Attention/executive f** | Vitality | 31,9 | 53,3 | 0,025 |
| | Mental Health | 36,0 | 62,5 | 0,006 |
| **Recovery Visual functions** | General health | 35,3 | 58,5 | 0,016 |
| | Vitality | 34,5 | 54,5 | 0,021 |
| | Social Functioning | 38,8 | 61,2 | 0,008 |
| | Mental Health | 41,2 | 62,2 | 0,021 |
| **Mood Disorders** | General Health | 40,1 | 66,5 | 0,001 |

| | | | | |
|---|---|---|---|---|
| | Vitality | 37 | 62,1 | 0,000 |
| | Social Functioning | 39,8 | 70,8 | 0,000 |
| | Role limitation emotional problems | 25,4 | 71,4 | 0,000 |
| | Mental Health | 43,6 | 71,4 | 0,000 |
| | | | | |

## *5.4 CONCLUSIVE REMARKS*

Aim of Study 1 was to investigate the prevalence and the association of mood disorders (MD) with specific clinical and anatomical features related to the brain tumour itself and with the patients' cognitive outcome, in order to further investigate the influence of CD and MD on HRQoL, before and after treatments.

Results of the analysis on 116 patients showed that:

- After treatments (surgery and adjuvant therapy) the incidence of MD, and particularly depression, increases.
- No association was however found between demographics or clinical characteristics of the population and prevalence of MD; for example, counter intuitively no significant effect of the grade of tumours on emergence of MD was found, as expected: the HG and LG patient's tumours show indeed similar prevalence of MD.
-The emergence of MD does not appear to be caused by a direct effect of the brain tumour, but rather seem to be caused by the consequences of the treatments, i.e. the neural deficits following surgery and /or adjuvant therapy. Regarding surgery this plays a minor role in this study given that when resection is performed with the BMt in a qualified team, as happened in for patients enrolled in this study, the prevalence of post-surgical neurological and CD is actually very low.
- MD do not correlate to the occurrence of deficits, but rather the significant association was found between the emergence of MD and the lack of recovery from CD and neurological deficits, and specifically the language, attentive/executive and visual deficits. This is not surprising in that these deficits, and particularly the visual impairment, lead to inabilities dramatically constraining the self-sufficiency of patients. The lack of association between deficits and MD before treatment, supports the hypothesis that the lack of recovery from deficits, frustrating the patient's expectance of a "restitutio in integrum" by the surgical procedure, triggers the emergence or worsen the MD.

As stated above, the emergence of MD is relevant for treatment in brain tumour patients, in that it negatively influences the patient's HRQoL especially at long term (3 and 6 month after treatments); specifically patients that during the months following surgery and adjuvant treatments do not recovery from their CD thus developing MD, show a worse HRQoL with respect to patients

regaining their cognitive and psychological “abilities” in the short term. Notably, while the impact on HRQoL of the neurological deficits that recovered within the second month following the surgery (that is the case of Motor deficits, because the team developed in time high skills in mapping procedure avoiding permanent deficits in almost all patients) is transient, the impact of deficits, requiring significantly longer time to recover (that is the case of Cognitive deficits), is dramatic and chronic. At 3 and 6 months the effects of motor deficits indeed disappear, while the effect of visual and some cognitive disorders such as executive and language deficit remains stable over time. Moreover, not all the cognitive deficits impact to the same extent on the HRQoL: among the cognitive deficits particularly importance has the visual deficits, given that is the lack of recovery from this specific deficit that, in association with MD, worsen to the highest extent the HRQoL across all SF-36 dimensions assessing especially the Mental Health experience.

In conclusion overall, the results of the first study suggest that it is not the actual cognitive or neurological loss that plays a significant role in the emergence of MD and in the subsequent decline in HRQoL, but the “expectancy of patients” on their recovery. Irrespective of the nature or gravity of deficits *per se*, if the patient does not improve over time, as expected based on the medical team information or previsions delivered before the treatment, he/she will develop more easily, a reactive MD that, in turn, will affect the subjective perception of HRQoL and, eventually the compliance and survival. Based on this evidence, while with no doubts the survival and the progression free survival must be considered the primary goal of brain cancer treatment for healthcare team, the HRQoL should not be neglected and more effort in developing strategies aimed at preventing and managing the relevant symptoms correlating with MD needs to be invested in this peculiar population of patients.

Therefore, in the next Chapters (6 and 7) two new intra-operative tools/tests developed in order to reduce the incidence of the specific cognitive deficits triggering MD, will be presented.

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# *STUDY 2-3: PRESERVING EXECUTIVE AND VISUAL FUNCTIONS DURING SURGERY FOR GLIOMA: NEW INTRAOPERATIVE TOOLS*

## *GENERAL INTRODUCTION TO CHAPTERS VI AND VII*

In gliomas, the use of Brain Mapping techniques and awake surgery allows to define tumour margins in order to maximize resection, reaching total and, when feasible, even a supratotal resection impacting on patient's survival, progression free survival and on the time to malignant transformation while preserving functional integrity (Smith *et al.*, 2008; Yordanova *et al.*, 2011). At present, intraoperative brain mapping is used to monitor motor, language and more recently also praxis abilities (Bello *et al.*, 2014; Duffau, 2014; Rossi *et al.*, 2017). However, the results of Study 1 (see Chapter V) on the emergence of MD in brain tumour patients, and the impact of MD on the quality of life, showed clearly that is not the occurrence of cognitive deficits (CD) per se that correlates with MD and HRQoL, but rather is the lack of recovery from CD and, among those, specifically the deficits of executive and visual functions. Based on these premises, it seems mandatory to preserve the global patient's functionality and thus the associated HRQoL during surgery and treatments. Motor and praxis deficits do not impact significantly on emergence of MD and HRQoL because the intraoperative BMt implemented with adequate intraoperative tools allow to maximizeing the resection while preserving the functional integrity and, indeed, the post-surgical deficits are transient fitting the expectation of recovery of the patients. Consequently, in order to achieve the same clinical results, the first intervention to impact on MD and HRQoL in brain tumour patients must be aimed at–expanding at most the number of neurological functions to be mapped and preserved during surgery. For these reasons, Study 2 and 3 were aimed at developing two new intraoperative tools to preserve the Executive Functions and Visual Functions, as described in the first part and second part of this chapter respectively.

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# *CHAPTER VI*
# *STUDY 2 "PRESERVING EXECUTIVE FUNCTIONS DURING SURGERY FOR GLIOMA: A NEW INTRAOPERATIVE TOOL".*

## *6.1 INTRODUCTION TO STUDY 2*

Executive functions (EFs) are defined as complex cognitive abilities necessary to select and monitor behaviors, to reach specific goals and for successful social interactions. In everyday life EFs are needed in conditions where it is required to focus on a specific behavior despite distractions or temptations, or to make a plan for the future, or voluntarily switch from one activity to another. Particularly, EFs play a crucial role in activity such as self-monitoring, initiation, inhibition, and planning. Studies of patients with acquired brain injuries suggested that, EFs are mediated by a complex frontal cortico-striatal network connecting prefrontal cortices and the basal ganglia (Garavan *et al.*, 1999; Konishi *et al.*, 1999; Braver *et al.*, 2001; Bunge *et al.*, 2001; Rubia *et al.*, 2001; Munakata *et al.*, 2011; Ouellet *et al.*, 2015). In fact, patients with lesions affecting this network (mainly Orbito-Frontal Cortex and Lateral-Pre Frontal Cortex) showed impulsive behavior (Winstanley, 2007) and difficulties to inhibit irrelevant stimuli in order to accomplish a cognitive task.

An explorative retrospective analysis of a series of patients undergoing supratotal resection for non-dominant frontal glioma from 2014 to 2015 (see below) showed a relevant prevalence of EFs deficits after tumour removal. This impairment was characterized by inappropriate and/or perseverative behaviors and by limitations in performing tasks requiring high attentive level, divided attention and reasoning. At long-term these deficits negatively affected the patient's everyday life, impairing the ability to work and to study or to develop and maintain appropriate social relations (Knouse *et al.*, 2013). Such evidence raised the need to implement the current brain mapping protocols by incorporating specific tasks aimed in testing and reducing the occurrence of post-surgical executive dysfunctions, while maintaining the main functional and oncological goal.

Efficient executive functioning requires the integration of a series of interrelated high–level cognitive processes (such as selective attention, inhibitory control, working memory, speed processing, and mental flexibility - (Diamond, 2013)). Such components are investigated separately by different neuropsychological tests (for details see section "Neuropsychological assessment"). Critically, because of setting limitation that characterizes awake surgery procedure, the goal of

Study 2 was to develop a test with a good balance between the feasibility in the intraoperative setting and the sensitivity to different executive components. To this aim we developed a simplified intraoperative version of the Stroop test (iST), a well-known task often applied in clinical context to assess some crucial component of EFs, i.e. inhibition of pre-potent automatic responses, cognitive flexibility and selective attention (MacLeod, 1991; Stuss *et al.*, 2001). This new version appeared to be quite easy and fast to administer in surgical setting, allowing the neuropsychologist to assess EFs continuously during the procedure while a direct stimulation was applied, at both cortical and more interestingly subcortical level, and use to define additional functional boundaries. The feasibility and ability of the simplified version (iST) in preserving EFs was evaluated in a series of patients with non-dominant frontal gliomas admitted in our service during the last two years underwent awake surgery with the additional use of iST, comparing the results obtained in this group with a balanced group of patients who underwent resection without the use of this intraoperative mapping tool.

## *6.2 MATERIALS AND METHODS*

### *6.2.1 PARTICIPANTS*

A total of 45 patients affected by a glioma and candidate for tumour resection during the awake-asleep-awake surgery with the aid of BMt were enrolled. The population of patients analyzed in the study was composed by two groups:

- *Stroop Group* (enrolled from second part of 2016-to 2017): 27 patients (16 women, mean age 37,8; SD 11,9; range 22-60; median education 15 years; IQR 13-17; range 13-17) who underwent standard BMt and iST
- *Control Group* (enrolled from 2015-to fist part of 2016): 18 patients (8 women, mean age 37,8; SD 14,4; range 23-77; median education 13 years; IQR 13-17; range 8-17) who underwent standard BMt without the administration of iST.

Inclusion criteria for both groups were: 1) glioma located in the right frontal lobe; 2) absence of language and visual deficits; 3) normal scores in pre-surgical EFs assessment (Stroop test performance, see below). The two groups were balanced for demographics and tumour characteristics as reported in table 1. The study was performed with strict adherence to the routine procedure adopted for surgical tumour removal.

*Table 1. Demographic and clinical features of the patients at baseline*

| CHARACTERISTICS | STROOP GROUP | CONTROL GROUP | P-VALUE |
|---|---|---|---|
| **No. of Patients** | 27 | 18 | |
| **Sex (%)** | | | .374 |
| Male | 11 (40.7) | 10 (55.6) | |
| Female | 16 (59.3) | 8 (44.4) | |
| **Mean age in years (+/- SD)*** | 37.8 +/- 11.9 | 37.8 +/- 14.4 | >.99 |
| **Median years of education (range)**** | 15 (13-17) | 13 (8-17) | .235 |
| **Seizure at presentation (%)** | 18 (66.7) | 11 (61.1) | .758 |
| **No. of AEDs (%)** | | | |
| 1 | 14 (51.85) | 12 (66.7) | |
| 2 | 7 (25) | 4 (22.2) | |
| **Median KPS score at presentation (range)** | 100 (80-100) | 100 (90-100) | .818 |
| **Histology (WHO 2016) [22]** | | | |
| **WHO Grade II (%)** | 18 (66.7) | 7(38.9) | |
| Astrocytoma | 10 | 3 | |
| Oligodendroglioma | 8 | 4 | |
| **WHO Grade III (%)** | 9 (33.3) | 10 (55.6) | |
| Astrocytoma | 5 | 5 | |
| Oligodendroglioma | 4 | 5 | |
| **WHO grade IV (%)** | | 1 (5.6) | |
| Glioblastoma multiforme | - | 1 | |
| **IDH-1/ IDH-2 mutated (%)** | 25 (92.6) | 17 (94.4) | .807 |
| **Mean lesion volume in $cm^3$ *** | 33.5 +/- 46.9 | 44.2 +/- 38.3 | .429 |
| **N° Supratotal resection + GTR (%)** | 23 (85.2) | 18 (100) | .138 |
| N° of Supratotal resection | 21 | 15 | .721 |
| N° of GTR | 2 | 3 | |
| **N° of subtotal resection (%)** | 4 (14.8) | - | |
| **Median EOR in % (range)** | 100 (83.3-100) | 100 (100-100) | .099 |

*AED = anti-epileptic drug; KPS = Karnofsky Performance Status; WHO = World Health Organization; IDH= isocitrate dehydrogenase; GTR = Gross Total Resection; EOR= extent of resection; * Mean values are expressed ± standard deviation (SD).*

### *6.2.2 NEURORADIOLOGICAL CHARACTERISTICS*

During preoperative period all patients were submitted to the specific neuroradiological evaluation as described in the Chapter IV (see par. *4.2.3.1).* Post-operative lesion volume was computed ( par. *4.2.3.1 and 4.2.3.2*) and volumetric analysis was used to define tumour volume (Smith et al. 2008). Mean lesion volume was 44,18 $cm^3$ (SD 38,3 range 2,3-142,3 $cm^3$) in Control group and 33,4 $cm^3$ (SD 46,9, range 1-211 $cm^3$) in Stroop group. The mean pre-operative volume was not statistically different between the two groups (gl=42; p=0,429).

### *6.2.3 ASSESSMENT OF EXECUTIVE FUNCTIONS (EFS)*

All patients in both groups (Stroop and Control group) were submitted to extensive pre-operative (1 week before surgery) and post-operative (7 days and 3 months after surgery) neuropsychological assessment (see Chapter IV section "4.2.4 Neuropsychological Assessment").
For the assessment of the EFs we have selected a group of tests proven to be sensitive to assess different components of executive functions:
-Raven Progressive Matrices Test (Basso et al. 1987) to assess non-verbal reasoning (ability to reason by analogy to make inference);
- Attentive Matrices Test (Spinnler et al. 1987) for the selective attention (ability to selectively react to certain stimuli while suppressing attention to other non-relevant concurrent ones);
-Trail Making Test (Giovagnoli et al.1996) for divided attention (ability to switch between or pay attention to two simultaneous subtasks);
- Verbal Fluency test (Novelli et al. 1986) for the lessical access speed and monitoring ability (ability to generate specific words and to suppress irrelevant responses and repetition).
-Digit Span Backward Test (Monaco et al. 2015) for working memory functions (ability to manipulate selected information and mentally working with it);
- Stroop Test (Caffarra et al. 2002) for resistance to interference, cognitive flexibility and inhibition of overlearned responses in favor of unusual ones (for the description of the tests see Chapter IV section 4.2.4 Neuropsychological Assessment).
With particular regard to Stroop Test, literature reports that patients with frontal lesions show slowed responses and increased errors in the Color–Word sub task (interference condition) in which subject have to inhibit the automatic tendency to read the written color (for example "blue") in order to name the incongruent color of ink in which the word is written (red) (Stuss et al. 2001). Because of its sensitivity for the identification of frontal lobe lesions assessing cognitive control continuously every 1-2 second, as is requested during an intraoperative assessment, an adapted version of Color–Word sub task was used during the intraoperative mapping of executive functions (Figure1; for details about the intraoperative administration see below section "*Intraoperative mapping and stimulation sites).*

### *6.2.4 SURGICAL PROCEDURE*

In both groups, the surgical resection was performed according to functional boundaries with the aid of BMt in order to perform a supratotal resection whenever was feasible. The

craniotomy to expose the tumor area and a limited amount of surrounding tissue was tailored. In Control Group motor (Bello et al. 2014), sensory-motor integration (Rossi et al. 2017) and language were mapped (Bello et al. 2014), while in the Stroop group iST was implemented and added to the previous mapping tools to identify sites involved in EFs, at both cortical and subcortical level. In the awake phase, cortical mapping was used to define the cortical safe entry zone. Subcortical mapping was performed to locate at the beginning of the procedure, before starting tumor resection, the functional boundaries at the periphery of the tumor (language and motor functions in the Control group; language, motor functions and EFs in the Stroop group). When subcortical tracts were identified, and the tumor functionally disconnected, the mass was finally removed under general anesthesia. During the intraoperative Stroop test (iST) the DES was applied with a Low Frequency (LF) paradigm (60Hz) or a High Frequency (HF) paradigm (To5, Repetition rate 3Hz) set at the same current intensity adopted for language mapping (2.75±0.93 mA). To avoid the risk of seizures, the LF-DES was substituted with HF-DES (Riva et al. 2016) in patients (n=4) in whom LF was ineffective in producing any language or motor cognition disturbances when applied over the vPM, even at high current intensity (Riva et al. 2016). In four patients both LF and HF paradigm were consecutively applied on the same sites.

### *6.2.5 INTRAOPERATIVE MAPPING AND STIMULATION SITES*

The iST is composed by an adapted simplified version of the Color-word subtask of the Italian brief version of Stroop Test. Specifically, only one item at time was presented in a 9,7'' monitor and the patients were asked to report as fast as they could the color of the hue of the observed word. Figure 1 illustrates the intraoperative test design. The brain mapping procedure was video-recorded and reviewed postoperatively by surgeons and neuropsychologists in order to verify the stimulation sites and the corresponding responses. In accordance with the usual procedure adopted in brain mapping during awake surgery (Ojemann 1989; Duffau et al. 2002) a stimulated site was considered *positive* when stimulations of that site interfered with the correct execution of the task at least three nonconsecutive times. We considered as errors those trials in which patients reported the written word instead of reporting the color or they showed latencies largely greater than average response time (1 sec). Patients' responses were given verbally and the neurosurgeon was immediately informed of the errors by the neuropsychologist who was fully blinded to the neuroanatomical location of the stimulation site. Each site tested during iST performance was also

evaluated for language (naming and semantic association tasks) or motor interferences to exclude overlapping.

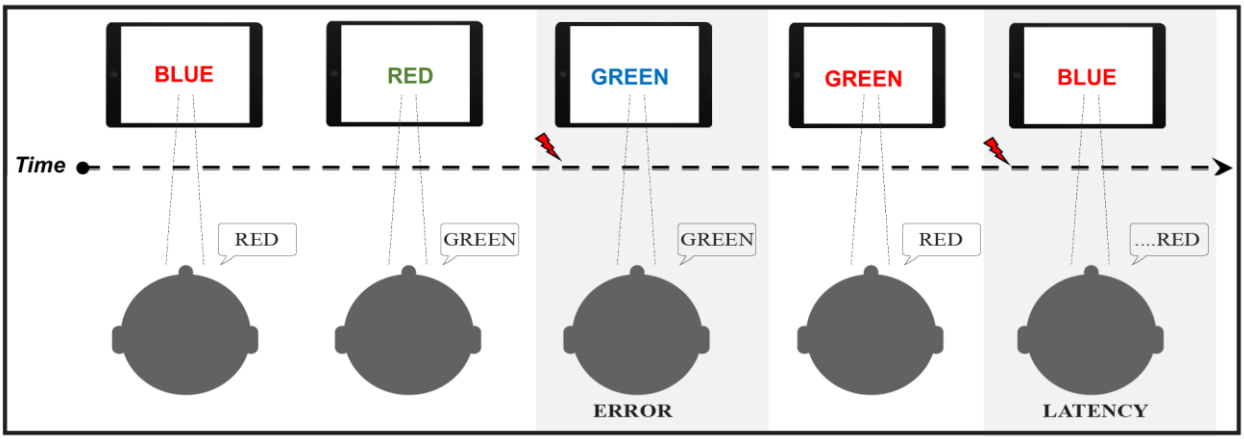


*Fig 1 iST Intraoperative task: it consists in an adapted version of Stroop test (iST); one word at time was presented in a 9,7'' monitor and the patient was asked to name as fast as he/she could the color of the ink of the observed word presented into the monitor (upper part of the figure). The response of the patient is reported in the bottom bubble. The red lightning represents the time at which the DES was applied over the investigated site. The duration of the stimulus was 2-3 seconds(s). When the patient reads the word instead the color the neuropsychologist reports "error"; when the time of the correct response is longer than the expected response time the neuropsychologist reports "latency".*

### *6.2.6 NORMALIZATION PROCEDURE AND STATISTICAL ANALYSIS*

During the intraoperative procedure, in accordance with patient's responses, the positive sites (i.e. the subcortical site that stimulated induced errors in iST) were acquired, when possible, by means of a neuronavigator (BrainLab) to co-register pre-operative T1-weighted MR with the stereotactic intraoperative position of the patient's brain. To minimize the error induced by the brain shift, the acquisition of positive site with the neuronavigation was performed at the end of the subcortical mapping procedure, before the resection of the tumor. Briefly, during the awake phase of surgery we performed the cortical mapping to identify the entry site, then the surgeon proceeded subcortically, disconnecting the tumor without resecting it, until a positive site was found. At this point all the positive sites identified were acquired by the mean of neuronavigation, correcting the position of sites by using of intra-operative US (Aloka). Subsequently the surgeon removed the tumour. The positive sites were verified offline, after surgery, through a video recording and then normalized in a MNI space by means of the affine transformation implemented in SPM8 software (Ashburner et al. 2005). In order to evaluate the efficacy of the iST at each time point (pre, immediate post-operative and 3 months after the surgery) the number of subjects who showed at least one sub-normal test was compared between Stroop and Control groups. Patients' continuous

variables were reported as mean ± standard deviation (SD) or median and compared with Student's t test. Categorical variables were compared with the Fisher exact test. We considered statistically significant a two-side P-values<0.05. A commercially available statistical software was used to perform the statistical analysis (SPSS statistics 22.0 for Mac; IBM SPSS Inc., Chicago, IL).

## *6.3 RESULTS*

### *6.3.1 FEASIBILITY*

The iST was successfully and completely administered intraoperatively in all 27 patients of the Stroop Group, without encountering any difficulties in its administration by the neuropsychologist or in its execution by the patient. The iST was successfully applied either in mapping with LF-DES (23 patients) or with HF-DES (4 patients). The duration of the test was 4 minutes (range 3-5) cortically and 7 minutes on the average (range 5-8) subcortically. Globally, the administration of iST increased the duration of the mapping of 11 minutes (range 8-13). Global mapping time during the awake phase of the surgery was 23 minutes (range 20-27). iST was administered by using the same intraoperative tool used for giving language mapping (9,7" tablet device).

### *6.3.2 INTRAOPERATIVE FINDINGS*

iST was applied either during cortical and subcortical mapping. Interestingly, no site positive for interference were registered cortically when iST was administered when DES was stimulating the inferior, medial or superior frontal gyrus (IFG, MFG or SFG). Subcortically, the location of positive sites, i.e. sites that when stimulated interfered with iST execution (see methods) were registered in each patient intraoperatively by the use of intraoperative navigation corrected with intraoperative US to reduce the effect of brain shift. Most of positive sites were located in a discrete subcortical area within the white matter of the non-dominant frontal lobe, running under the IFG and MFG, in front of the anterior insula, and lateral to the head the caudate, passing on the putamen and the anterior thalamus to reach the cingulum. The location of one of these sites is reported in a representative example in Figure 2. In most of these sites the patient produced a color-word inversion (65%) or, less frequently, latency i.e. a longer delay in responses (35%). Notably in the same sites, DES did not produce any interference during motor, motor cognition or language

task. Language and motor cognition task were alternated with iST during subcortical mapping, to define posterior and inferior margin of resection. Language disturbances were identified in only 4 out of 27 patients, always in different sites with respect to those involved in iST. HF-DES and LF-DES produced the same interferences in each sites.

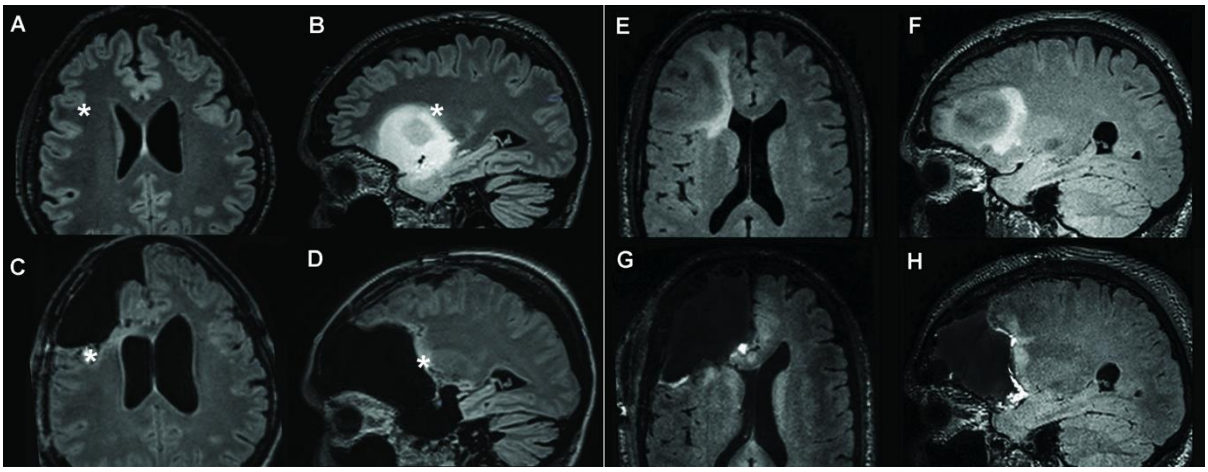


*Fig. 2. Representative MR images of two cases of LGG located in the non-dominant frontal lobe. (A-D): Stroop Group (A-B pre-operative axial and sagittal FLAIR, C-D post-operative axial and sagittal FLAIR); (E-H): Control Group (E-F: pre-operative axial and sagittal FLAIR; G-H: post-operative axial and sagittal FLAIR). The white asterisk (*) in A-D represents the location of a positive site that gave interferences at DES while the patient was performing the Stroop Test; resection was stopped at this site.*

### *6.3.3 NEUROPSYCHOLOGICAL OUTCOME*

Figure 3 reports, for both Stroop-Group and Control-Group, the percentage of patients showing a sub-normal score in at least one test of the neuropsychological battery at all time points (pre-surgery, 7 days and 3 months after surgery). No difference in EFs deficits between Stroop-Group (14.8%) and Control-Group (27.8%) (P= .449) were observed before surgery and at 7 days after surgery the Stroop patients showed a lower incidence of EFs deficits (51.9%) compared with Control patients (77.8%) (P= .07). The difference between the two groups further increased at 3 months after surgery, due to a decrease of incidence of EFs deficits in the Stroop-Group compared to Control-Group (22.2% and 61.1% respectively) (P= .01).

When specifically analyzing the subcomponents of EFs compromised in the long run (3 months post surgery), it emerged that the few Stroop patients showing EFs deficits were actually impaired only in in one subcomponent (verbal fluency: 85%; 6 out 7). On the other hand, nearly half of the Control patients (54%) showing EFs deficits were compromised in more than one subcomponent (digit span backward, Stroop test, verbal fluency). Interestingly, the deficit in digit backward test was significantly higher in Control-Group compared with Stroop-Group (33% versus 0%; P = .004).

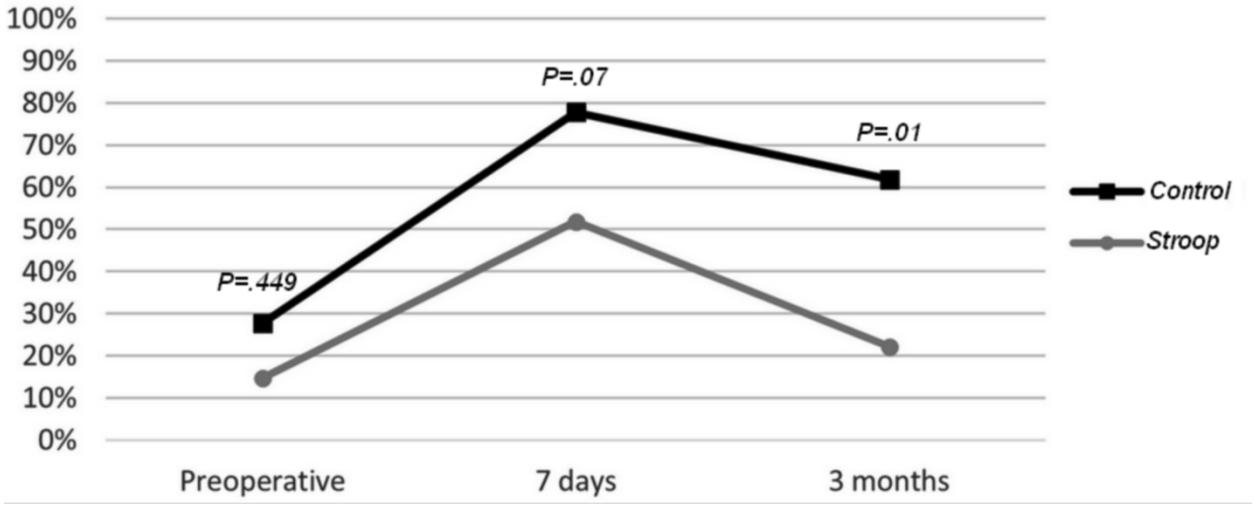


*Fig. 3. Trend of Executive deficits. Prevalence (as a percentage) of executive deficits measured 7 days before surgery (Preoperative), 7 days after surgery and at 3 months after in the patients belonging to the Stroop (grey line) or to the Control (black line) group. P represents the significance of the difference in EFs deficits between the two groups for each time point.*

### *6.3.4 Effect on EoR and intraoperative surgical strategy*

As it has been showed in Table 1, in most of patients of both groups we performed a supratotal resection, which largely exceeded the tumor volume. Consequently, the median EOR of the two groups were not statistically different (Stroop group 100% range 83,3-100, Control Group 100% range 100-100, p = 0,099. See Table 1), providing evidence that the use of iST did not significantly impact on EOR. On the other hand, while in the Control Group the posterior margin of the resection was coincident with the location of subcortical motor or, less frequently, language responses or was based on anatomical landmarks (such as the ventricle or the insular cortex), in the iST group, the finding of subcortical positive sites during the iST administration helped in defining a posterior and deep margin of the resection, that were not previously identified, as it is shown in a representative example in Figure 2 (A-D) preventing deficits but not reducing the effect of the resection.

## *6.4 CONCLUSIVE REMARKS*

This study moved from the observation that patients treated by our team during 2015 for non-dominant frontal lobe tumor in which resection was performed by using standard intraoperative mapping tools, despite the integrity of language and motor functions, showed specific EFs impairments. Specifically, at 3 months after surgery in about 61% of patients the neuropsychological assessment revealed the occurrence of deficits in at least one of different neuropsychological tests associated with the specific components of EFs. Despite such deficits are often underestimated, they can produce important difficulties in the management of complex situation making harder for the patient to go back to the daily routine activities in a very high efficient manner with a negative impact on their HRQoL. Previous and recent studies highlighted the role of specific connectivity network running in the inferior frontal lobe in mediating EFs deficits in some pathological conditions, such as autism (Catani et al. 2016). Based on the hypothesis that such deficits are caused by intraoperative resection of such still unidentified subcortical pathways contributing to the modulatory activity of prefrontal cortices, we evaluated the feasibility and the efficacy of an intraoperative version of the Stroop task (iST) in localizing and preserving such functional related structures during frontal tumor resection. Stroop test is a well-known neuropsychological test evaluating some crucial component of EFs (Stuss et al. 2001; MacLeod et al. 1991). Moreover, it allows assessing cognitive control continuously every 1-2 second, as it is requested during the intraoperative assessment. The main results were that:

- High feasibility of the iST during awake mapping: iST was easily administered by the neuropsychologist, and did not require the implementation of additional tools, being given by the same instrument used for language mapping (9,7" tablet pc). It was also easily performed by the patients, as shown by the fact that all patients were able to execute and complete the task entirely.
- High intraoperative efficacy of the iST. To evaluate the intraoperative efficacy of the iST in identifying sites involved in EFs performance, we applied DES at cortical and particularly subcortical level in different sites within the frontal lobe, while the patient was executing iST. Consistently with our hypothesis, DES applied over the white matter of the frontal lobe leaded to a temporary disruption of the ability to maintain the rule of the task during its execution in several discrete sites. It resulted in clear errors (color-word inversion) or, less frequently, in a greater time of responses (latency). Notably, DES over the same sites didn't produce motor responses (of hand or mouth), interference with motor cognition or language task (naming, semantic association) suggesting a high specificity of the tool and at the same time of the sites identified by this test.

- High clinical efficacy of the iST. The clinical efficacy was also demonstrated by the fact that neuropsychological evaluation 7 days post-surgery showed that patient who performed iST had a lower prevalence of EFs deficit. Crucially, as showed by results of post-operative assessment at 3 months after surgery, the iST dramatically decreased the prevalence of long-term post-operative deficits in EFs. Specifically, as shown by analysis of single tests performances, in the long-run working memory appears to be the most preserved component of EFs by the use of iST, while it appears less suited to preserve lexical access speed. Interestingly, iST identified a quite discrete subcortical area running from the IFG and MFG to the anterior insula, lateral to the head of the caudatus and over the putamen to reach the cingulum.

Globally considered, these results are consistent with clinical and experimental data about the role of frontal white matter in cognitive control (Aron et al. 2007; Forstmann et al. 2008; Seghete et al. 2013; Lipszyc et al. 2014; Schmahmann et al. 2007). Recent studies correlating subcortical tracts changes and emotional or behavioral disturbances in autism, highlighted the role of frontostriatal or anterior thalamic connections, as well as inferior insular connectivity in such alterations (Langen et al. 2012). However, further studies are needed to dissect intraoperatively the specific involved tracts or subcortical structures.

The iST seems to be effective in define a further discrete functional boundary, located in the deep, posterior white matter of the non-dominant frontal lobe. By the implementation of iST resection at the posterior margin of the frontal lobe could be performed according to function and not to classical anatomical landmarks. This result did not impact on the EOR, in that the mean EOR in the two group of this study did not show statistically significant difference. The relevance of the introduction of the iST allowing the identification and respect during resection of iST eloquent site at the posterior margin of the frontal lobe, lead to EFs preservation, particularly in cases, such as low-grade gliomas, in which a large resection is planned and the expectancy of life is long.

Overall, our data suggested that the iST is a feasible and reliable candidate to identify and preserve intraoperatively the networks underlying EFs, and helpfully reducing higher order cognitive disorders associated with supratotal resection of right frontal lobe tumour.

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# *CHAPTER VII*
# STUDY 3 "PRESERVING VISUAL FUNCTIONS DURING SURGERY OF GLIOMA: A NEW INTRAOPERATIVE TOOL"

## *7.1 INTRODUCTION TO THE STUDY*

Brain tumors and related resection involving temporal, parietal or occipital lobe can induce permanent visual field deficits such as *quadrantanopia* and/or *hemianopsia* due to damage to the optic radiations or to the visual cortex. Precisely, the *quadrantanopia* corresponds to a visual anopia (i.e. defect of the visual field) affecting only one of the quadrants of the visual field while the *hemianopsia* is a visual defect of half of the visual field (Fig. 1)

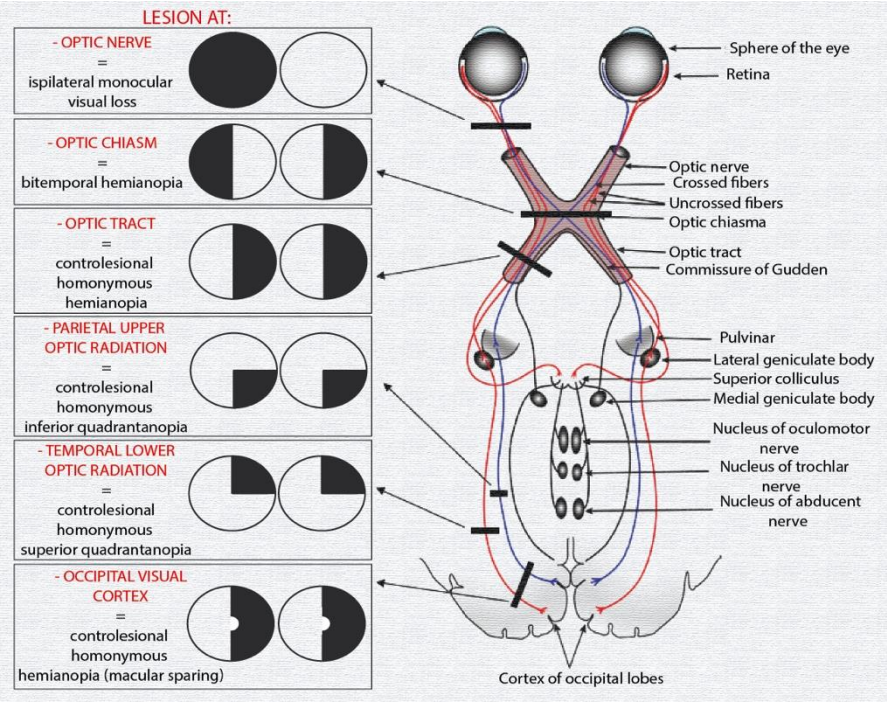


*Fig. 1. Visual Fields Defects: in the right part of the figure the representation of visual system; in the left part we show specific visual defects caused by the specific lesions of the visual system.*

Commonly hemianopsia results form lesions of the occipital lobe (45%), followed by lesions of the optic radiations (32%), lesions of the optic tract (10%), lateral geniculate nucleus (LGN) (1.3%), or a combination of several areas (11%) (Zhang et al. 2006). A lesion of the LGN can causes defects in one or more sectors of visual field, since the lateral portion represents the superior visual field, and

the medial portion represents the inferior visual field. Temporal lobe lesions tend to cause superior visual field quadrant defects while parietal lesions are more likely to cause inferior visual field defects (Fig.1). Specifically, surgical resection of anterior part of temporal lobe with a consequent damage to Meyer's loop, the most anterior part of the optic radiation, causes visual field deficit in 48% to 100% of patients (Jeelani et al. 2010).

The impairment of the visual field is often underestimated by the clinicians but can be, particularly hemianopsia, debilitating for the patient's daily living. In fact, while the functional disability caused by quadrantatanopia is minimal, permanent hemianopia has a significant impact on the patient's quality of life (QoL) because impairs the performance of many everyday life activities such as the ability to drive or read and/or to evaluate the environment. Patients with hemianopsia show longer visual scanning times than patients with normal visual field, because they make more saccades toward the blind field, but the saccades are less accurate and systematic with respect to the saccades towards the non blind field (Zihl et al. 1998). This slowness of visual scanning time causes patient's disorientation, because do not allow an efficient and fast inspection of the environment to detect or avoid obstacles and hazards increasing risk of falling inducing, for example, difficulties in trouble crossing the street in traffic or detecting objects. These limitations cause a significant decrease of independence, inability to work, limits employment opportunities, or to enjoy leisure activities increasing the risk of depression (Ragland et al. 2005). The results regarding MD reported in Chapter 5 confirm that it is particularly the persistent visual field impairment that impacts significantly on psychological and social implications with a negative effect on patient's mood and HRQoL.

In recent years, great effort have been focused in developing increasingly sophisticated methods for mapping optic radiations intraoperatively in order to reduce the risk of visual field defects or at least to reduce the severe visual defects to a quandrantanopia. Despite this effort, at present there are few reliable approaches available in the literature and they are rarely performed because of the difficulty of testing the visual field in the intraoperative setting (Wolfson et al. 2015). The main approaches so far described during surgery are: 1) neuronavigation based on tractography; 2) visual evoked potentials (Kamada et al. 2005); 3) direct subcortical stimulation in awake patients and virtual reality headset (Mazerand et al 2016). The use of tractography of the optic tract loaded on the neuronavigation system available for the surgeon, was reported to efficiently reduce the severe visual defects during anterior temporal lobe resection for temporal lobe epilepsy (Winston et al. 2014). However, this approach is not reliable in the tumour surgery because peritumoral oedema alters the visualization of the white matter tracts on diffusion tractography and the brain-shift,

caused by the tumour mass, can be only partially corrected by intraoperative MRI guidance. Another approach consists to try to use the visual evoke potential (VEP) to monitor the visual cortex under general anaesthesia, recording the visual evoked potentials with subdural electrodes and photic stimulation through closed eyelids with a strobe light (Curatolo et al. 2000). Postoperative visual field testing showed preservation of central vision, although with some reduction in peripheral fields. Nevertheless, several studies showed different limitation of this technique. First, the variability of the potentials in the intraoperative setting makes the VEPs an unreliable technique for intraoperative monitoring. Second, it has been demonstrated that intraoperative VEPs may be attenuated in patients with poor pre-operative visual acuity. Third, this approach requires an optimal balance of other factors such as anaesthesia, possibly altering the excitability of the cortex and thus the feasibility and reliability of the technique (Rajan et al. 2016).
Differently with respect to the approaches described above, the direct cortical and subcortical electrical stimulation (DES) that is the gold standard techniques for resection of intra-axial lesions, might be proposed as the gold standard to preserve the visual filed abilities. However, so far BMt was rarely aimed at preservation of visual function and the tools available at present, not feasible and accurate. Duffau and colleagues (2004) first reported the attempt to map with DES the visual pathways in awake craniotomy during a resection of tumour located at the temporo-occipital junction, asking to the patient, (Duffau et al. 2004) to report the occurrence of visual problems during stimulation. In a second study the same group used a double picture naming task with presentation of two objects situated diagonally on a screen (Gras-Combe et al. 2012). An image was presented in the quadrant to be saved, and another image was presented in the opposite quadrant and the patient has to name both images. This tool is a promising instrument to avoid lesions involving the sagittal stratum of the dominant hemisphere because language tracts and optic radiations are very close within the temporo-occipito-parietal junction, (stimulation of the language pathways would result in naming disturbances for the both pictures, whereas misnaming only 1 of the 2 pictures would be linked to a visual disturbance). However, the size of images used for the intraoperative test did not allow to define, accurately, the portion of visual fields that patient's does not perceive, because the images seems to fall both in the foveal vision. More recently some authors tried to adapt the tools using virtual reality to map the visual tracts (Mazerand et al. 2016) during awake surgery, by asking to the patients to detect (saying yes or no) a luminous stimulus (green dot) on the screen divided in 4 quadrants, while the neurosurgeon performed brain mapping with DES. Again, although the promising approach the test used and specifically the detection of the coloured dot, is unreliable because it is not possible to assess whether the patient's answer is a

random occurrence or not. Altogether the data acquired by the past clinical efforts, demonstrated that despite some progress, there is still the need to develop a precise tool to correctly map the visual tracts and to reduce the visual field deficits.

For this reason, our group developed a new "visual intraoperatory tool" (iVT) to map optic radiation during awake surgery for resection of supra-tentorial brain tumour. In Study 3 we evaluated the feasibility, safeness and reproducibility of this intraoperative tool in 25 consecutive patients.

## *7.2 MATERIALS AND METHODS*

### *7.2.1 PARTICIPANTS*

Twenty-five consecutive patients with a tumor involving visual pathways candidate for surgical resection in awake surgery with the aid of BMt were enrolled between December 2016 and April 2018. The patients were included in this study based on the following inclusion criteria: 1) intra-axial lesions involving optic radiations, specifically lesions located in temporal lobe, parietal lobe, lesions temporo-parietal junction and occipital lobe, or 2) intra-axial lesions, which surgical approach could include optic radiations. The group was composed by 10 males and 15 females (mean age 42 ± 2,19 years), the tumour was located in right (12 cases) and left (13 cases) hemisphere with different localizations and different histological diagnosis (for details see Table 1)

*Table 1: Clinical, radiological, and surgical patient's characteristics.*

| *Case No.* | *Age; gender* | *Hand.* | *Lobe* | *Side* | *Toumor Grade* | *T.Vol. pre ($cm^{2}$)* | *EoR %* |
|---|---|---|---|---|---|---|---|
| *1* | 37; M | R | P | R | LGG | 32,346 | 100,0 |
| *2* | 53; F | R | P | L | LGG | 21,121 | 100,0 |
| *3* | 40; M | R | T-O | L | LGG | 18,824 | 89,5 |
| *4* | 53; F | R | T | L | LGG | 4,248 | 100,0 |
| *5* | 30; F | R | F-T-I | L | HGG | 68,688 | 100,0 |
| *6* | 44; F | R | F-T-I | L | HGG | 55,063 | 100,0 |
| *7* | 26; F | R | T | R | LGG | 4,394 | 100,0 |
| *8* | 40; M | R | P-T | R | LGG | 53,450 | 90,2 |
| *9* | 36; M | R | T-I | R | LGG | 95,333 | 87,5 |
| *10* | 49; M | L | P-T | L | LGG | 7,580 | 100,0 |
| *11* | 46; F | L | I | R | HGG | 29,757 | 100,0 |
| *12* | 66; M | R | T | L | HGG | 9,098 | 100,0 |
| *13* | 48; F | R | T | L | LGG | 0,878 | 100,0 |
| *14* | 30; F | R | F-T-I | R | HGG | 144,520 | 99,5 |
| *15* | 67; F | R | T | R | GBM | 2,851 | 100,0 |
| *16* | 50; F | R | T | L | HGG | 10,002 | 100,0 |
| *17* | 42; F | R | T-O | L | LGG | 2,113 | 100,0 |
| *18* | 37; M | R | T-O | L | LGG | 5,243 | 83,7 |
| *19* | 41; M | R | T-I | L | HGG | 39,509 | 100,0 |
| *20* | 42; M | R | F-T-I | R | HGG | 35,166 | 100,0 |
| *21* | 26; M | R | O | R | LGG | 0,758 | 100,0 |
| *22* | 49; F | R | T-I | R | HGG | 75,547 | 100,0 |
| *23* | 33; F | R | F-T-O | R | HGG | 94,812 | 100,0 |
| *24* | 31; F | L | P-T | R | LGG | 102,799 | 97,1 |
| *25* | 37; F | R | P-T-I | R | HGG | 96,529 | 100,0 |

Legend: M= Male; F= Female; Hand.= Handness; R= Right; L= Left; F= frontal; I= insular; P = Parietal; T= Temporal; O= Occipital; HGG= High Grade Glioma; LGG= Low Grade Glioma; T.vol.pre= Toumor Volume pre-surgery; EoR = Extent of resection.

### *7.2.2 NEURORADIOLOGICAL FEATURES*

During preoperative period all patients were submitted to the specific neuroradiological evaluation (see Chapter IV) to define location and anatomical relationships of the tumour with the surrounding cortical and subcortical areas (e.g. dislocation, infiltration) (see par. *4.2.3.1).* Post-operative lesion volume was computed as described in the chapter 4 (see par. *4.2.3.1 and 4.2.3.2*). Volumetric analysis was used to define tumour volume (Smith et al. 2008): mean lesion volume was 40,43 $cm^3$ (SD 8,18).

### *7.2.3 ASSESSMENT OF NEUROLOGICAL, NEUROPSYCHOLOGICAL STATUS AND VISUAL FIELD CAPABILITIES*

All subjects underwent an extensive neurological and neuropsychological evaluation during pre and post-operative period, (pre- 5 days, 1 month and 3 months postsurgery (for details see Chapter 4, section 4.2.4 "Neuropsychological Assessment") in order to assess the cognitive profile and to verify the reliability of the responses to the visual assessment.

Visual examination performance was performed using Confrontation visual field test in all case and, for the last consecutive 10 patients, Humphrey field analyser (HFA) was used. All the patients were evaluated, with the confrontation visual field test, each day during the post-operative period (7-10 days after surgery) for the eventually onset of new visual deficits.

### *7.2.4 SURGICAL PROCEDURE*

Surgical resection was performed under asleep-awake-asleep anesthesia according to functional boundaries with the aid of BMt. The craniotomy to expose the tumor area and a limited amount of surrounding tissue was tailored. In all the patients the new iVT was done to map and recognize optic radiation; according to site of the lesion other intraoperative test was performed. In awake phase, cortical mapping was used to define working current and the cortical safe entry zone. Subcortical mapping was performed to locate, at the beginning of the procedure and before starting tumor resection, the functional boundaries at the periphery of the tumor. When subcortical tracts were identified, and the tumor functionally disconnected, the mass was finally removed under general anesthesia. During the iVT the DES was applied with a Low Frequency (LF) paradigm

(60Hz) delivered by a constant current stimulator (OSIRIS Neuro Stimulator) integrated into the ISIS system.

Tumour histology and molecular pattern were classified based on the WHO Classification of Tumours of the Central Nervous System. A post-operative MRI was performed 48/72 hours after the surgery to evaluate EOR and identify any post-operative complication.

### *7.2.5 Intraoperative visual test (iVT): tracts mapping and stimulation sites*

We predispose an innovative intraoperative test to map the visual system, which is applied during the awake phase of the surgery. Intraoperative Visual Task consist in a presentation of three different target numbers – 0, 3 or 7 – that appears one at time, randomly, for 0.5 seconds, on the left or right part of the tablet screen, while the subject is instructed to fix a cross positioned at the centre of his field vision. The patient has to recognize a series of target numbers, which fall in the upper, lower, or middle portion of his visual field periphery, specifically contralaterally to the lesion (Figure 2). Different numbers are chosen in order to verify, for each trial, that the patient's response is consistent with the trial avoiding false positive or negative responses. The numbers 3, 0 and 7 are chosen because is different in shape, in order to avoid inducing errors based on the similar shape of the numbers (for example 1 and 7; 3 and 8; 0 and 9).

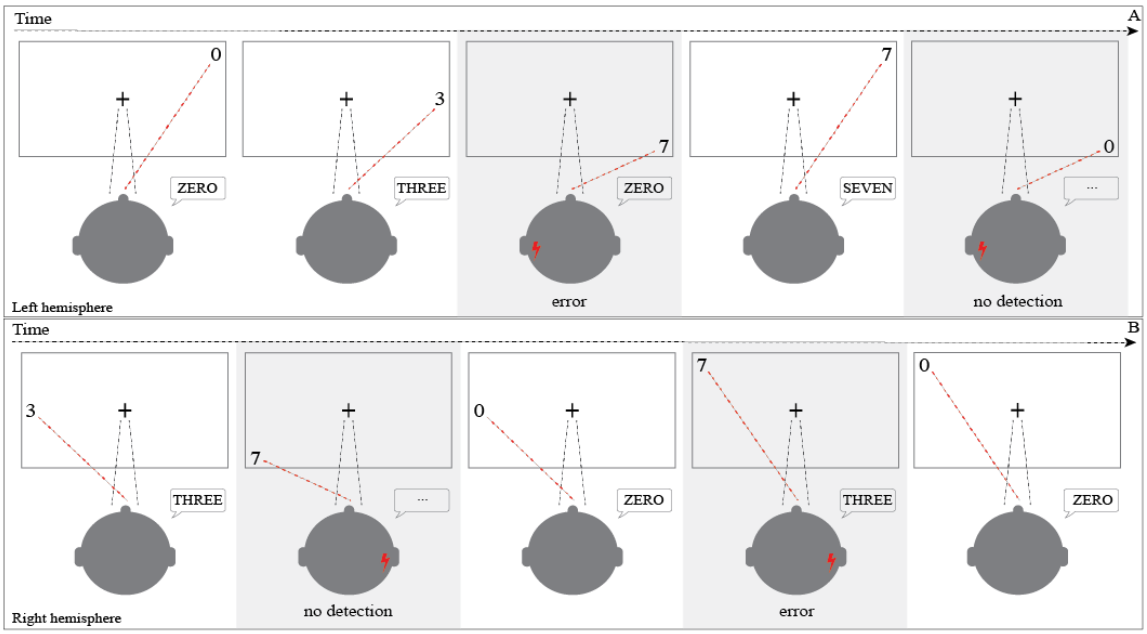


***Fig.2*** *iVT Intraoperative task: one number at time was presented in a 9,7'' monitor and the patient was asked to name the number presented in the upper, lower, or middle (randomly) position of the monitor to allow the investigation of each quadrant of the visual field. In the upper and lower part of the figure the left and right hemisphere condition is respectively reported. The response of the patient is reported in the bubble; dots indicate no responses. The grey square and red lightning represent the time at which the DES was applied over the investigated site.*

During mapping procedure, all extraneous noise (suction tubing, pulse oximeter volume, etc.) are reduced to a minimum, and the patient is equipped with a microphone to ensure that the surgical team can hear all responses. The tasks are administered and controlled by a trained neuropsychologist. The visual task is usually used to recognize deeper, posterior and mesial boundaries of lesion located in temporal lobe and lesion located in Temporo Occipital Junction. it is integrated with other intraoperative test routinely used by our surgical team based on location of the lesion (i.e. HMt, semantic association, naming, iST.). If the lesion is located in parietal lobe the iVT is administrated to recognize visual tract in the caudal part of the lobe; we usually switch iVT with HMT during resection of lesion located in the parietal lobe. Stimulation is given just before the task appears. A site is considered to be positive if stimulation-induced errors are present for at least three times.

## *7.3 RESULTS*

Results showed that the iVT was fully reliable to identify, intraoperatively, the visual structures in 100% of cases allowing us to maximize the EOR. The post-operative analysis of peripheral visual assessment showed that 17 of 25 (68%) patients did not show any post-operative visual deficits; 2 of 25 (8%) resulted in a postoperative hemianopia, and only 6 of 25 (24%) showed quadrantanopia (Fig. 3). These deficits, however, were predicted by the surgeon and voluntarily generated (hemianopia in 1 case and a quadrantanopia in all 6 cases), in order to extend as much as possible the resection. In most of patients (Table 1) the surgeon performed indeed a supratotal resection (median EOR is 97,9 ± 0,9 mm^3).

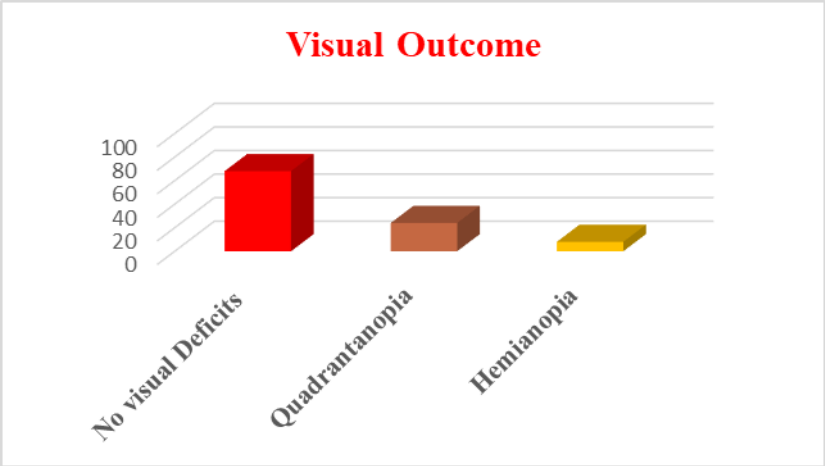


*Fig.3 Visual Outcome: bars show percentage of patients with visual deficits: red bar no deficit; brow bar quadrantanopia; yellow bar hemianopia.*

## *7.4 CONCLUSIVE REMARKS*

The BMt allows to maximizing the tumour removal preserving functional structures in order to dramatically reduce the impairment of the cognitive functions. Language and sensori-motor functions have, over time, received more attention respect to the other functions, due to the negative impact that aphasia or motor deficits have on the patient's quality of life. For a long time, other functions have been neglected and only recently the need to develop it is proposed intra-surgical tools for mapping of networks not involving language or motor functions has been recognized to improve the functional patient's outcome. Specifically, deficits in visual field is a postoperative disability that has been largely underestimated in neurosurgery even though surgical damage to Meyer's loop results in a visual field deficit in 48% to 100% of patients (Jeelani et al. 2010). Such damage significantly impacts on patients' life, precluding driving, reading activities and reducing the social interaction with a relevant impact on the emergence of MD and in turn on the HRQoL. Preservation of visual ability seems particularly relevant to allow patients to maintain a normal lifestyle. Based on this evidence and inspired by the observation that patients with hemianopia showed a higher level of MD compared to the patients with other deficits, we developed and evaluated the feasibility and the efficacy of a new intraoperative visual task (iVT) designed to localize and preserve the optical radiations during tumor resection.

Results support the efficacy of the new tool for the main clinical purpose, being feasible and accurate.

- The new iVT is indeed highly feasible in the intraoperative setting and easy to administer by the neuropsychologist, and did not require the implementation of additional tools, being given by the same instrument used for language mapping (tablet pc). It was also easy to be performed by the patients, as shown by the fact that all patients were able to execute and complete the task entirely. These features are crucial for an intraoperative tool.
- The new iVT allows to identify, intraoperatively, the visual structures in 100% of cases, avoiding the hemianopia in 92% of the cases, and preserving complete visual field in most of the patients (68%).

This test appears a reliable and promising approach to mapping optic radiations and preventing permanent visual field defects in brain tumour surgery leading in MD and in reduction of HRQoL.

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# *GENERAL CONCLUSION*

This thesis reports the results of a novel research study (Study 1) investigating the incidence of Mood disorders (MD) and their impact on Health-Related Quality of Life in the peculiar population of patients affected by of brain tumour patients. The demonstrated correlation between MD and cognitive deficits and particularly with Executive functions and Visual deficits, in a second study (Study 2 ans 3) specific clinical interventions were developed aimed at avoiding the occurrence of MD, in turn impacting on the HRQoL, to improve the patient's prognosis.

Results of the analysis about the occurrence of MD, performed on 116 patients (Study 1), showed that after treatments (surgery and adjuvant therapy) the incidence of MD, and particularly depression, increases (10% before treatments vs 40% at 6 months after treatments). Disregarding the claim of the main recent literature (Jenkins et al.2014; 2016), our data showed that the demographical (age and education) and clinical characteristics of the tumour (grade and laterality) are not related to the occurrence of MD, as intuitively expected. Overall the results suggest, instead, that MD in brain tumour patients correlate to the consequences of the treatments, i.e. the neural (cognitive) deficits following surgery and/or adjuvant therapy. The incidence of MD does not correlate with the occurrence of neural deficit s in general, but specifically, the main predictors of the occurrence of MD were shown to be the lack of recovery from language, attentive/executive and visual deficits. Interestingly, the absence of association of MD with clinical variables and with neural deficits already affecting patients before treatments, supports the hypothesis that MD are primarily a psychological mediated responses to the lack of recovery from deficits. In fact the disappointment of patient's expectance of a *restitutio in integrum* by the oncological treatments, triggers the occurrence or worsen the MD. The specific association of incidence of MD with language, executive/attentive and visual deficits is not surprising, in that on one side these deficits did not recover in the course of disease following treatments, compared to other deficits, like motor impairment, that recover in time. On the other side, the persistence of these language, executive/attentive and visual deficits, lead to inabilities that dramatically constraining the patients' self-sufficiency. Furthermore, our results showed that the emergence of MD and the persistent daily life limitations, negatively affect the patient's HRQoL especially at long term (3 and 6 months after treatments). Specifically, patients that during the months after surgery and adjuvant treatments do not recover from their cognitive/neurological deficits thus developing MD, show a worse HRQoL with respect to patients regaining their cognitive and psychological "abilities" in the short term. The

impact on HRQoL of the neurological deficits that recovered within the second month following the surgery (as the motor deficit) is transient, while the impact of deficits, requiring significantly longer time to recover (cognitive deficits and visual deficit), is dramatic and chronic. This result reflects the fact that the main dimensions of the HRQoL are the physical and social well-being, i.e one's ability to perform the activities related to one's personal needs, ambitions, or social role and to the maintenance of leisure activities and family functioning. In conclusion Study I showed that, irrespective of the nature or gravity of deficits *per se*, if the patient does not improve over time, as expected based on the medical team information or previsions delivered before the treatment, he/she will develop more easily, a reactive MD that, in turn, will affect the subjective perception of HRQoL and, eventually the compliance to treatments and survival. These results add novel evidence to the available literature reporting studies on MD in brain tumour patients highlighting not only the significance of clinical evaluation and follow-up of psychological symptoms among brain tumour patients before and after tumour treatment, but also the patient's distress to tolerate the limitations caused by the lack of recovery. Unfortunately, some deficit as language, attentive and visual deficits are unlikely to be recovered in a short time. For this reason, Study 2 and 3 were aimed at increasing the efficacy of the Brain Mapping Technique developing two novel tools aimed at reducing the incidence of attentive/executive and visual deficit triggering MD and impacting on HRQoL. Study 2 and 3 (Chapter VI and VII) showed that the new intraoperative tools, and namely the intraoperative stroop test (iST) and intraoperative visual test (iVT), are feasible, accurate and reliable methods to identify and preserve the brain network subserving the attentive/executive and visual abilities during the surgical resection of the tumour. Specifically, the implementation of the iST (Chapter VI) lead in a dramatic decrease in the prevalence of long-term post-operative deficits in attentive and executive functions without compromising the Extent of resection. Similarly, regarding the visual abilities, the post-surgical assessments showed that the new iVT allows to identify, intraoperatively, the visual structures in 100% of cases, avoiding deficits in the patient's visual outcome, as hemianopia, preserving complete visual field in most of the patients.

Conclusively, the novel evidence provided by the Study 1 was that is not the cognitive deficit *per se*, but rather the patients' expectation about their recovery after surgery/treatment and their disappointment that play a crucial role in determine the emergence of MD consequently negatively affecting their HRQoL. These results suggest the importance of a proper communication of predicted deficits by the medical team.

On the other hand, Study 2 and 3 highlighted the feasibility of a more accurate BMt using new intraoperative tools allowing for the increase of the EOR without affecting patient's functional

integrity (Study 2 and 3). Overall this research suggests that the efficacy of a neurooncological treatment should account for both the neuropsychological outcome of treatments and also patients' expectation, delivering them realistic information and thus expectations, about their post-treatment outcome.

## *FUTURE PERPECTIVES*

With no doubts, the survival and the progression free survival must be considered the primary goal of the treatment of brain tumour patients by the healthcare team. However, results of my project highlighted that the psychological implications and the effect on the HRQoL, of the neuro-oncological treatments, should not be neglected. The physical, functional, emotional, and social needs of brain tumour patients must be at best taken into account by adoption of synergic strategies aimed at preventing and managing cognitive and neurological symptoms. The implementation of novel tools in BMt has been shown to be feasible and effective in reducing some deficits with an important effect on the patient's well-being reducing the impact on the primary goal of the surgery i.e good balance between oncological and functional aim.

Unfortunately, sometimes, despite the efforts, the main oncological aim prevents to preserving the patient's functionality or ensuring patients to return to their life in a short time, according to their expectations. The First Study clearly demonstrated that that the lack of recovery of language deficits is one of the main factors predicting MD and worse HRQoL. Nevertheless, in recent years, great effort has been focused in developing increasingly sophisticated methods for mapping intraoperatively the language function in case of left tumour – especially temporal and parietal lobe lesions – but mild language impairments are often inevitable.

In the light of the results obtained, my future research will be focused on:

-developing new and more efficacy communicative approach to manage the patient's expectancy;

-investigating language deficits. At present, using voxel-based lesion symptom mapping (VLSM) and Diffusion Tensor Imaging (DTI), we are investigating which are the anatomical predictors of poor language recovery following surgical intervention in brain tumour patients, with the aim to better understand the language network and the role of both hemisphere on the language functions. Results of this study will provide new evidence to be used to avoid language inabilities to patients.

The actual impact of both the new communicative strategies and the new intraoperative tools on the HRQoL will be assessed to provide conclusive remarks.