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SUBCORTICAL VASCULAR DAMAGES FOR POST RADIATION BRAIN RADIOTHERAPY

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ABSTRACT

In the last decades radiotherapy induced brain injury has become an emerging issue for physicians. Brain RT-induced injury has been classified, according to its time of onset, into acute, early delayed, and late forms. The latter is not reversible. Etiopathogenesys of brain damage after RT has been at length discussed, vascular injury and white matter pathologic changes have been described. In our study we described the neurological cognitive and behavioural disruption produced by radiotherapy in primary brain neoplasia; moreover we demonstrated that the effect of radiation on the brain has a classic time dependent course, with a severity related to total radiation dose, individual fraction size, and the volume of brain irradiated. The patients, who suffered from the consequence of RT, did show slowness of executive functions, and profound alterations of frontal functions, such as attention focusing, mentation control, analogical judgement and insight, not differently from those obtained by the patients suffering from subcortical vascular dementia. The overall result of high dose- RT might be a severely demented, bedridden patient, who "has been cured" for his primary disease, the brain tumour, but it constrains us to make serious consideration before radiation therapy onset and in order to implement new strategies to avoid this damage.

INTRODUCTION

Long considered a major concern in pediatric neuro-oncology (Hall *et al*., 2004; Spiegler *et al*., 2004; Byrne, 2005), treatment-related neurocognitive sequelae have recently become increasingly recognized in adult neuro-oncology (Taphorn *et al*., 2004; Moretti *et al*., 2005; Sarkissian, 2005; Byrne, 2005; O'Neill, 2004).Cranial radiation, used in the treatment of primary brain tumors, cancer metastatic to brain, certain head and neck malignancies and historically in the management of acute leukemia, may result in a debilitating neurological dysfunction (encephalopathy, headache, seizures, visual loss, cerebellar toxicity) and cognitive syndrome (cognitive deficits that include dysfunction of episodic memory, deficits in speed of information processing and executive functions such as attention and calculation). (Ruben *et al* 2006; Wefel *et al*., 2004; Taofeek *et al*., 2014). Symptoms may be especially accentuated in long-term survivors of cancer treated with both radiation and chemotherapy.

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All the published reports of severe cognitive impairment in long-term anaplastic glioma survivors describe patients who received whole brain RT (usually 4,000-4,500 cGy) plus a focal tumor boost (Imperato *et al*., 1980; Barker *et al*., 2003). A potentiating effect of nitrosoureas or other chemotherapy on the neurotoxic effect of RT has been postulated (Klein *et al*., 2002; Dropcho, 2003). Following the Radiation Therapy Oncology Group agreement the maximal tolerated dose for targets 31–40 mm in diameter should be 15 Gy, and for targets 21–30 mm in diameter, 18 Gy. Anyway data are different among studies mostly because of the differences in the definitions of the volume and toxicity, the avoidance of critical structures, and the type and length of clinical follow-up. Regarding the fractionated RT, for twice-daily fractionation, a steep increase in toxicity appears to occur when the biologically effective dose (BED) is >80 Gy, while for daily large fraction sizes (>2.5 Gy), the incidence and severity of toxicity is unpredictable (Murray *et al*., 1997; Cheung *et al*., 2000; Yaacov *et al*., 2010; Hsiao *et al*., 2010). Ionising radiation causes damage by a double-stranded DNA bandage, by damage to RNA, proteins, lipids and cellular membranes, by inducing calcium inflow, stimulating apoptosis by

mechanisms not completely understood (Paleologos, 2000; Monje and Dietrich, 2012). In the EORTC and Medical Research Council (MRC), an end to the controversy on the efficacy of postoperative RT for adult patients with cerebral LGG was sought in a randomized trial (EORTC 22845/MRC BR04) that was initiated in 1986. The EORTC Radiotherapy Cooperative Group, the EORTC Brain Tumor Group, and the Brain Tumor Working Party of the MRC (UK) participated in this trial (Karim *et al*., 2002). This study was planned in the early 1980s with conventional RT techniques with baseline clinical and CT scan data. In general, the debate on early post-operative RT continues and shall continue to dominate the policy of treatment for some time. The interim results of the EORTC study indicate the reasons why one group of specialists does not believe in postoperative early RT and the believers in RT routinely use early postoperative radiation. From their personal experience, the nonbelievers in RT find that the outcome scores of these patients without early postoperative RT is equally justified, because the hazards of radiation sequelae from the literature are well known. Moreover, they consider that delayed RT might be equally effective.

The series of well conducted studies, in rodents and human brain exposed to radiotherapy, demonstrated that a particular area, the so-called subventricular zone (SVZ), might be a focused target for RT (Monje and Dietrich, 2012; Zhao *et al*., 2008; Chang *et al*., 2000; Dawson *et al*., 2003; Geha *et al*., 2010; Kempermann *et al*., 1997; Eriksson *et al*., 1998; Van Praag *et al*., 1999). SVZ area maintains a specific role in adult brain too, throughout the lateral walls of the alteral ventricle: along with the dentate gyrus of the hippocampus and the olfactory bulb, the SVZ is one of the three places, where neurogenesis has been found to occur in the adult mammalian brain (Quinonones-Hinojosa *et al*., 2007). Human SVZ stem cells may contribute to neurogenesis in yet-unknown forebrain regions, and also may replenish glial precursor populations throughout the white matter. Oligodendroglial precursor cells are found throughout white matter and contribute to postnatal myelination, particularly in the frontal lobes, which do not complete myelination until the third decade of life. Impairment of hippocampal neurogenesis may explain the profound difficulties patients experience encoding new episodic memories following treatment for brain tumors and other cancers requiring cranial radiation therapy. Cranial radiation therapy profoundly inhibits the generation of new hippocampal granule cell neurons in both rodents and in humans (Monje *et al*., 2012). Of note, radiation does not simply ablate the hippocampal stem and precursor pool, but rather alters the neurogenic microenvironment. Radiation-induced activation of local microglia and the subsequent elaboration of pro-inflammatory cytokines such as interleukin-6 produce a specific blockade in neuronal differentiation. This micro environmental perturbation can be mitigated by non-steroidal anti-inflammatory therapies, offering a possible clinical intervention for patients suffering from radiation- induced memory dysfunction (Monje *et al*., 2002; Monje *et al*., 2012) Elsewhere preclinical and clinical evidence showed that radiation dose received by the neural stem cells of the subgranular zone in the hippocampus may play a role in radiation induced neurocognitive decline, specifically memory recall. Dosimetric capabilities of intensity-modulated radiotherapy to conformally avoid the hippocampus without detriment to the radiation dose received by the remainder of the brain has been detected.

Hippocampal sparing during whole brain radiotherapy (WBRT)-largely employed up to ten years ago for brain lymphomas, for example, may provide a net gain in control neurocognitive decline (Vinai *et al*., 2010; Johannesen *et al*., 2003; Welzel *et al*., 2008; Brown *et al*., 2007; Junie *et al*., 2013). Autopsies in a few patients showed diffuse injury to myelin sheaths with relative preservation of axons and large blood vessels (De Angelis *et al*., 1989). The Radiation Therapy Oncology Group was working on a dose-escalation study aimed to define the maximal dose for targets of different sizes; generally the volume of brain receiving ≥12 Gy has been shown to correlate with both the incidence of radiation necrosis and asymptomatic radiologic changes and the presence of comorbid vascular risk factors (e.g., diabetes) (Lee e t al., 2002; Wong *et al*., 2004). Radiation-induced brain injury is described as acute, early delayed, and late delayed injury (Greene-Schloesser *et al*., 2012). Between several different hypotheses of late radiation-induced brain injury the vascular hypothesis has been strongly described; it seems that vascular damage leads to ischemia and secondarily to white matter necrosis. Vascular structural changes, as vessel wall thickening, vessel dilation, and endothelial cell nuclear enlargement have been reported. Similarly, capillary rarefaction and tissue hypoxia increased after fWBI. Beside the vascular hypothesis the parenchymal hypothesis has been explained involving oligodendrocytes, astrocytes and microglia role in generating a pro-inflammatory mediators and subsequent radiation-induced edema (De Angelis *et al*., 1989; Vigliani *et al*., 1999).

The diffuse sufferance of the white matter in radiation induced neuronal damage is comparable to that seen in subcortical vascular dementia (Abayomi, 1996). Immunohistochemical examination of the brains without necrosis found myelin basic protein-positive fibers were markedly decreased in the affected areas by irradiation; neurofilament-positive fibers were moderately decreased and irregularly dispersed in various shapes in the affected areas, and glial fibrillary acidic proteins-positive fibers were increased, with gliosis in those areas. These findings are similar to those in clinically accelerated brain aging in conditions such as diffuse subcortical ischemia, previously called Binswanger's disease. Novel studies have been done to assess neuroanatomical targets of radiation-induced cognitive decline. It has been found that regions that predicted global cognitive outcomes at doses 60 Gy included the corpus callosum, left frontal white matter, right temporal lobe, bilateral hippocampi, subventricular zone, and cerebellum. Regions that did not predict global cognitive outcomes at any dose include total brain volume, frontal pole, anterior cingulate, right frontal white matter, and the right precentralgyrus. (Peiffer *et al*., 2013). Despite efforts to isolate cognitive effects due to partial RT alone, prior longitudinal studies have not consistently controlled for several potential confounding influences including surgical effects, effects of underlying disease progression, and practice effects resulting from serial neuropsychological testing. With these considerations in mind, the current study evaluated longitudinal cognitive functioning in the first 12 months following modern highly conformal fractionated partial brain RT. This work is an implementation of that written by our group (Moretti *et al*., 2005). We have enrolled 87 new patients, after having studied 34, described elsewhere (Moretti *et al*. 2005). Overall the hypothesis of cognitive decline due to radiotherapy is interesting, but not unexpected data; however, the comparison and the items taken into account are for the

first time compared to those obtained by a group, early-diagnosed as suffering from subcortical vascular dementia. A part from the previously employed tests, which we have reproduced in this work, we have tested more specifically two distinct aspects apathy and gait and equilibrium. The purpose is to define and study the potential common frontal white matter sufferance indirectly determined by radiotherapy, not deriving from tumor location, but to the involvement of subcortical networks sufferance, and strictly resembling subcortical vascular dementia.We present the results after the 12-months follow-up of 87 RT patients.

METHODS

Patients

We have followed 87 cases (51.2 ± 7.3 yrs. old) of primitive cerebral neoplasia, surgically treated; all of them underwent to radiotherapy (group A). They were enrolled as admitted in Neurological Units Section, to be studied and then prepared to neurosurgery; they were not part of other clinical trials. Patients were not included in the study if they showed previous signs of non-lacunar territorial infarcts, normal pressure hydrocephalus, cortical hemispheric large vessel strokes or lobar hemorrhages. Patients with previous psychiatric illness or central nervous system disorders and alcoholism were also excluded from the study. Patients with focal Broca or Wernicke's area brain tumors were also excluded due to major, confounding linguistic impairment. Control subjects were 90 men and women, (69.75 ± 2.34 yrs. old) (group B), entering in Cognitive Disorder Unit Evaluation of the University of Trieste, with Mini-Mental State Examination (MMSE) scores of at least 16 and satisfying the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for dementia, recruited from June 1st 2010 to June 1st 2013, suffering from subcortical vascular dementia: these study subjects satisfied the criteria for probable VaD in accordance with the NINDS-AIREN criteria (Román *et al*., 1993). A patient was diagnosed as having subcortical VaD (sVaD) when the CT/MRI scan showed moderate to severe ischemic white matter changes (Erkinjuntti *et al*., 1997) and at least one lacunar infarct. All patients underwent a standardized baseline assessment that included a detailed history, a physical examination, laboratory tests and psychiatric evaluations. Psychiatric evaluations (which later formed the study's outcome measures) are described below. All patients were followed for 12 months, with periodical examinations. Visits were scheduled to take place 3, 6, and 12 months after the start of treatment. A complete neuropsychological examination was conducted at baseline, and at the last visit. The study was conducted in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute. Written informed consent was obtained from all participants or their responsible caregivers prior to the study.

Outcome measures

Though many works have tried to establish recommendations fora a core set of neuropsychological tests, common criterion for defining cognitive impairment and common approaches to improve the homogeneity of study methods, (Wardy *et al*., 2008; Wefel *et al*., 2011), the purpose of this study suggest us to implement some other batteries, in order to better define the frontal and prefrontal executive and behavior functions, and motor and balance measures. Global cognitive function was assessed using the MMSE (Folstein *et al*., 1975) at each visit. In addition, since the MMSE is not sensitive to changes in executive functions or mental slowing, attention was assessed using the number of correct responses in the Digit Span forward and backward (Wechsler, 1945), the number of substantives produced in a three-minute task for phonological and semantic fluency (Wechsler, 1981), and mental and written calculation (Paradis *et al*., 1990) and, Apathy Score (AES-S and C) at each visit (Marin *et al*., 1991). Behavioural symptoms were assessed using the Behavioural Pathology in AD Rating Scale, BEHAVE-AD (Reisberg *et al*., 1987) at every visit. Motor symptoms, concerning gait and equilibrium have been evaluated by Tinetti scale at each visit (Tinetti *et al*., 1996).

Statistical analyses

Statistical analyses were performed using SAS® software (version 16.0 SAS® Software Inc, Cary, NC, USA). Within-group changes from baseline were tested using the Wilcoxon Signed Ranks test. Between-group comparisons of changes from baseline were tested using the Marginal Homogeneity Test. Spearmann correlation test has been employed for each significant variable. This was done for each efficacy variable. Results are presented as mean changes from baseline with standard deviations, and p-values are provided where appropriate.

RESULTS

Patients

We have followed 87 cases (51.2 ± 7.3 yrs. old; + 22.34 at Briggs and Nebes Test (1975); 14.7 + 3.98 years of school) of primitive cerebral neoplasia (Group A), surgically treated/biopsied and anatomically diagnosed as follows: 17 cerebral lymphomas (mild- or low-grade differentiation), 24 cases of glioblastomamultiforme, 17 cases of grade-2 gliomas, 5 cranyopharingioma, 15 II-III grade-astrocytomas and 9 anaplastic pattern. They underwent to neurosurgery; the surgical operations have been radical in 29% of cases; 31% of cases could be considered partially efficacious; 40% of cases surgery could be considered as a stereotaxical biopsy. All the cases in group A were submitted to radiotherapy: the patients underwent to fractionated external beam radiation therapy (from 20 to 65 cGy). Three patients had received a concomitant high-dosage Methotrexate therapy, i.v. and 18 themozolamide orally, concomitantly. We have chosen 90 sVAD patients. All the patients could be fully studied (mean age 72.3 ± 7.3 years, range= 62-94 years). The diagnosis was based on historical information and neuropsychological assessment and supported by findings on structural (CT or magnetic resonance) imaging. Subsequent follow-up of subjects has reinforced the clinical diagnoses in all cases. Brain CT-scans or MRI images were available for all the selected patients; 90 sVAD patients did CT scans and moreover, 21 of them completed the diagnostic pathway with MRI images, in case of not adequate imaging acquisition, or not convincing data. Therefore, the patients who did CT/MRI were homogeneously recruited and no demographical/social/ cultural/clinical difference distinguish from each other. A neurologist (RM) revised all the imaging, employing the Blennow *et al*. (1991) scale for CT scans and the Scheltens *et al*. (1993) scale for MRI imaging in sVAD patients. There was

95.8% inter-rater agreement for the independent assessment of the scans (kappa=0.8). Patients were allowed to continue any previous therapy (e.g. antihypertensive, antidyslipidemic, antidiabetic drugs). During the follow-up, the patients were prescribed neuroleptics and/or benzodiazepines; nobody has been prescribed Ache-I or memantine. All the surgery patients underwent to neuropsychological evaluation; one week before surgery, one week after surgery, while executing RT, 6 and 12 months after radiotherapy they underwent to neuropsychological tests. The first two sessions were dedicated to identify eventual decay of cognitive performances due to the tumor mass localization or to the brain injury consequent neurosurgery: patients from Group B attended the evaluation at the beginning, 6 and 12 months after the recruitment. At the end of the follow-up process (12.2 + 4.6 months), Group A was composed by:25 patients received a low dose of radiation (<30 Gy); 18 patients a medium dosage (30-45 GY) and among this group, 4 subjects died; 44 patients receive a cumulative dosage of more than 45 Gy up to 65 Gy; among them 8 subjects died.

The sub-group who received <30 Gy was composed by: 5 cranyopharyngiomas, 11 grade -2 gliomas and 9 astrocytomas grade 2; the sub-group who received 30-45Gy was composed by: 6 glioblastomamultiforme, 6 grade - 2 gliomas and 6 astrocytomas grade 2-3; the sub-group who received 45-65Gy was composed by: 17 lymphomas, 18 glioblastomamultiforme and 9 anaplastic tumours. Any patients underwent to WBRT: radiotherapists used regional fields partial brain, encompasses each tumor, with an average margin of 2.6 $\pm$ 0.7 cm from the initial target tumor volume. Therefore, in this study we have not considered the size tumor/radiation field ratio. 12 patients totally died during follow-up and they have been not taken into account for the final statistical analysis. No patients from Group B died. Results have been compared within groups (baseline versus 12 months follow-up) and between groups (low vs medium vs high dosage of radiation, and vs control group).

patients who received a cumulative dose of radiation <30 cGy did show specific differences when compared with sVAD, in phonological and semantic fluency, analogies, digit span backward, apathy at baseline (Table 2); at 12 months, but they did not show significant differences with baseline results, a part from a dramatic increase in apathy scores (as showed in Table 2 Group A got worse in semantic fluencies, analogies, apathy and Tinetti total scores); when compared at 12 months Group B did worse than A in phonological, semantic, analogies, Digit span Forward, apathy in Tinetti equilibrium, gait and total scores. 30 patients who received a total dose comprised between 30-45 cGy manifested a global slowness of cognitive process. Before the beginning of RT, they did worse than sVAD in mental calculation, analogies digit span backwards, apathy between groups, table 3, and second row).

They dramatically deteriorated in all the tasks a part from digit span and backwards (within groups at 12 months, table 3, third row). They did worse than sVad after 12 months (between groups, table 3, 5th row) in MMSE, in fluency tasks, in analogies, in apathy scores. All the patients, in both group showed an evident deterioration of walking strategies, evidenced by a patent disequilibrium, and gait alterations (significantly different within groups baseline vs 12months), not different between groups. 20 patients who underwent to high doses of radiotherapy (45 Gy-65 Gy) presented at baseline worse performances in all the items between groups (RT vs SVAD, 2nd row, Table 4). At 12 months they decreased their performances significantly (within groups, 3rd row, table 4); between groups at 12 months revealed more profound deterioration in RT patients than in sVAD in all the performances, more profoundly in apathy and gait scores. All the oncological patients underwent to MRI scans, after RT; the increase of white matter alterations, defined by white matter hyperintensity on the T2-weighted images, markedly on the periventricular regions was markedly evident from the 30-45 up to 45-65 Gy; in the last group, white matter hyperintesities on the T2 weighted images interested

Table 1. A synopsis of the scores obtained by the two groups at baseline group A, before RT; Apathy scores, AES-C, clinician rated apathy evaluation scale; AES-S, self-report rated apathy evaluation scale. Values are mean (SD). NS=not significant

Tests	Group A (before RT)	Group B (sVAD)
MMSE	28.34 ± 2.23	27.34 ± 2.34ns
Phon. Fluency (items produced)	45.67 ± 2.45	39.34 ± 3.56 ns
Sem. Fluency (items produced)	32.16 ± 2.56	27.34 ± 2.34 *
Mental calculation (correct /15)	11.4 ± 2.34	9.87 ± 1.34 ns
Analogies (correct/26)	24.56 ± 5.67	19.34 ± 2.45 *
Digit span forward	6.78 ± 2.34	4.56 ± 2.13*
Digit span backward	5.97 ± 1.23	4.03 ± 1.23*
BEHAVE-AD	4.56 ± 7.67	3.7 ± 0.34
AES-S	10.5 ± 1.1	12.1 ± 5.3
AES-C	7.22 ± 2.1	15. 9 ± 1.2

p<0.05 vs RT group; ** p<0.01 vs RT group

At baseline, patients in group B did worse than those of group A in semantic fluency, in analogies tasks and in the digit span forward/backward task (p<0.05). There was no significant difference in mental calculation, apathy and in behavior (see Table 1). Afterwards, we examined the results which have been summarized in Table 2, 3 and 4 and proceed by comparison between groups (Group A, divided by total dose, vs B at baseline; Group A divided by total dose at 12 months, versus baseline by Wilcoxon Signed rank test within group; Group B at 12 months, versus baseline by Wilcoxon Signed rank test within group; lastly, there is the differences between Groups at 12 months by Wilcoxon Signed Rank Test). 26

frontal subcortical areas and profoundly para-ventricular frontal areas. When compared between groups, we divided the process into three subitems: <30 Gyvs 30-45 and vs 45-65, and 30-45 vs 45-65 Gy (Table 5). When considering a marginal homogeneity test: The first subitem comprises the following results: MMSE average scores, phonological fluency, mental calculation, analogies, apathy were worse (mean MH statistics 498,00± 3.46; 663,00± 5.47; 562,00± 3.107; 633,00± 2.1; 612,00± 1.47, respectively, all p<0.01) than those of 30-45 Gy. Semantic fluency and digit forward were worse (mean MH statistics 562,00± 3.107 and 453,00± 5.47, respectively p<0.05); not significant the digit backward and BEHAVE

Table 2. A synopsis of the scores obtained by the patients of group A, who underwent to a total dose < 30cGy, at 12 month

Tests	Group A (RT) <30Gy	Group B (sVAD)	Group A 12 months/baseline	Group B 12 months/baseline	A vs B 12 months
MMSE	25.9 ± 1.7	26.34 ± 2.2	- 1.7 ± 2.1	-1.14 ± 2.1	-0.3 ± 1.0 NS
Phon. Fluency (items prod.)	40.1 ± 2.2	31.67 ± 2.4 *	-5.9 ± 2.4	-6.9 ± 2.4 **	-8.3 ± 1.4 **
Sem. Fluency (items prod)	34.5 ± 1.23	24.4 ± 1.4*	-5.4 ± 2.1*	-2.1 ± 6.4*	- 7.1 ± 1.4 **
Mental calculation (correct /15)	12.3 ± 1.4	11.8 ± 1.3	- 1.8 ± 1.3 ns	-0.87 ± 1.34 ns	-1.3 ± 1.1 NS
Analogies (correct/26)	19.2 ± 1.1	24.5± 5.6 *	- 1.6 ± 2.7 *	-3.56 ± 5.67 *	-6.3 ± 1.4 **
Digit span forward	6.7 ± 0.4	6.8 ± 2.3 ns	- 1.6 ± 2.13 ns	-1.56 ± 2.13 ns	-0.3 ± 0.1 **
Digit span backward	4.65 ± 0.7	6.1 ± 0.3 *	-0.3 ± 1.23 ns	-1.1 ± 0.2 ns	-0.7 ± 0.4 NS
BEHAVE-AD	3.1 ± 1.4	2.7 ± 0.4 ns	+1.7 ± 0.4 ns	+2.7 ± 0.3 ns	-0.8 ± 1.4 NS
AES-S	9.5 ± 1.4	12.1± 0.4**	+2.1 ± 0.4*	+6.1 ± 0.4**	+8.3 ± 1.2 **
AES-C	12.1 ± 1.4	15.9 ± 4.34 **	+5.1 ± 1.2 **	+7.1 ± 1.2 **	-7.3 ± 1.1 **
TINETTI equilibrium	13.1 ± 0.1	10.1 ± 0.1	-1.1 ± 0.5 ns	-3 ± 0.6 **	-4.3 ± 1.1 **
TINETTI gait	10.2 ± 1.1	10.2 ± 1.1	-1.2 ± 1.1 ns	-4.9 ± 1.1 **	-6.1 ± 1.4 **
TINETTI tot.score	23.3 ± 1.2	20.3 ± 1.2	-3.3 ± 1.6 *	-7.9 ± 0.2 **	-11.2 ± 1.4 **

Table 3. A synopsis of the scores obtained by the patients of group A, who underwent to a total dose 30-45Gy, at 12 month

Tests	Group A (RT) 30-45 Gy	Group B (sVAD)	Group A 12 mths/baseline	Group B 12 mths/baseline	A vs B 12 mths
MMSE	26.3 ± 1.2	26.34 ± 2.2	-4.64 ± 2.1 **	-1.14 ± 2.1	-2.3 ± 1.4 **
Phon. Fluency (items prod.)	29.3 ± 2.6	31.67 ± 2.4	-7.9 ± 2.4 **	-6.9 ± 2.4 **	-2.3 ± 1.4 *
Sem. Fluency (items prod)	26.7 ± 2.9	24.4 ± 1.4	-11.4 ± 5.4**	-2.1 ± 6.4*	- 7.1 ± 1.4 **
Mental calculation (correct /15)	6.7 ± 1.2	11.8 ± 1.3 **	-3.7 ± 1.4 *	-0.7 ± 1.4 ns	-1.3 ± 1.1 NS
Analogies (correct/26)	17.9 ± 4.1	24.5± 5.6 **	-6.6 ± 5.7 **	-3.56 ± 5.67 *	-9.4 ± 1.4 **
Digit span forward	4.9 ± 1.4	6.8 ± 2.3 ns	-1.6 ± 2.1 ns	-1.7 ± 2.1 ns	-1.6 ± 0.1 NS
Digit span backward	4.1 ± 2.2	6.1 ± 0.3 *	-2.1 ± 1.23 ns	-1.1 ± 0.2 ns	-0.7 ± 0.4 NS
BEHAVE-AD	5.84 ± 3.89	2.7 ± 0.4 ns	+2.9 ± 0.4 ns	+2.7 ± 0.3 ns	-2.8 ± 1.4 NS
AES-S	19.4 ± 1.4	12.1± 0.4**	+8.1 ± 0.4**	+6.1 ± 0.4**	-7.3 ± 1.2 **
AES-C	21.5 ± 1.4	15.9 ± 4.34 **	+9.3 ± 1.2 **	+7.1 ± 1.2 **	-8.3 ± 1.1 **
TINETTI equilibrium	12.4 ± 0.2	10.1 ± 0.1	-3.1 ± 0.3 **	-3 ± 0.6 **	0.3 ± 1.1 NS
TINETTI gait	10.8 ± 0.7	10.2 ± 1.1	-3.3 ± 0.7**	-4.9 ± 1.1 **	-0.4 ± 0.4 NS
TINETTI tot.score	23.2 ± 0.3	20.3 ± 1.2	-8.3 ± 1**	-7.9 ± 0.2 **	-0.5 ± 0.4 NS

* p<0.05 vs baseline; ** p<0.01 vs baseline;

Table 4. A synopsis of the scores obtained by the patients of group A who underwent to a total dose 45-65 Gy, at 12 month

Tests	Group A (RT) 45-65 Gy	Group B (sVAD)	Group A 12 mths/baseline	Group B 12 mths/baseline	A vs B 12 mths
MMSE	19.0 ± 2.7	26.34 ± 2.2**	-6.4 ± 1.1 **	-1.1 ± 2.1	-6.3 ± 1.4 **
Phon. Fluency (items prod.)	14.5 ± 1.7	31.67 ± 2.4 *	-7.9 ± 2.4 **	-6.9 ± 2.4 **	-15.3 ± 1.1*
Sem. Fluency (items prod)	13.2 ± 1.5	24.4 ± 1.4*	-4.4 ± 5.4**	-2.1 ± 6.4*	- 6.5 ± 1.4 **
Mental calculation (correct /15)	4.1 ± 0.2	11.8 ± 1.3 **	-2.7 ± 1.4 *	-0.7 ± 1.4 ns	-4.3 ± 1.1**
Analogies (correct/26)	12.2 ± 0.6	24.5± 5.6 **	-6.6 ± 5.7 **	-3.56 ± 5.67 *	-9.7 ± 1.4 **
Digit span forward	4.0 ± 0.8	6.8 ± 2.3*	-1.6 ± 2.1 *	-1.7 ± 2.1 ns	-3.6 ± 0.1 **
Digit span backward	3.6 ± 0.3	6.1 ± 0.3 *	-2.3 ± 1.2*	-1.1 ± 0.2 ns	-3.4 ± 0.4 **
BEHAVE-AD	5.7 ± 4.7	2.7 ± 0.4 *	+2.9 ± 0.4 *	+2.7 ± 0.3 ns	+6.8 ± 1.4 **
AES-S	21.8 ± 3.4	12.1± 0.4**	+18.1 ± 0.4**	+6.1 ± 0.4**	+24.3 ± 1.2 **
AES-C	25.2 ± 2.2	15.9 ± 4.34 **	+19.3 ± 1.2 **	+7.1 ± 1.2 **	+25.3 ± 1.1 **
TINETTI equilibrium	9.1 ± 0.1	10.1 ± 0.1	-3.1 ± 0.3 **	-3 ± 0.6 **	-0.6 ± 1.1 *
TINETTI gait	7.2 ± 1.4	10.2 ± 1.1*	-5.3 ± 0.7**	-4.9 ± 1.1 **	-0.4 ± 0.4 *
TINETTI tot.score	15.3 ± 1.5	20.3 ± 1.2**	-8.4 ± 1**	-7.9 ± 0.2 **	-0.5 ± 0.4*

* p<0.05 vs baseline; ** p<0.01 vs baseline

Table 5. A synopsis of the scores obtained by the three groups of RT patients at 12 month

Tests	Group A (RT) <30Gy	Group A 30-45 Gy	Group A 45-65 Gy
MMSE	24.2 ± 1.6 **; §§	21.3 ± 1.2 §§	12.1 ± 2.7
Phon. Fluency	35.2 ± 2.2 **; §§	19.7 ± 2.6 §§	7.5 ± 1.7
Sem. Fluency (items produced)	29.1 ± 1.3 *;§§	15.3 ± 2.9 §§	9.2 ± 1.5
Mental calculation (correct /15)	10.5 ± 1.4 **; §§	3.0 ± 1.2 §§	2.3 ± 0.2
Analogies (correct/26)	18.6 ± 1.1 **; §§	1.1 ± 4.1 §§	6.2 ± 0.6
Digit span forward	5.1 ± 0.4 *; §§	3.3± 1.4 ns	2.7 ± 0.8
Digit span backward	4.3 ± 0.7 ns; §§	2.0 ± 2.2 §§	1.6 ± 0.3
BEHAVE-AD	4.8 ± 1.4 ns; §§	8.7 ± 3.8 ns	9.6 ± 4.5
AES-S	12.6 ± 1.4 **; §§	27.5 ± 1.4 §§	39.8 ± 3.4
AES-C	17.2 ± 1.4 **; §§	30.8 ± 1.4 §§	45.2 ± 2.2
TINETTI equilibrium	12.0 ± 0.1*;§§	9.13 ± 0.4 §§	6.1 ± 0.8
TINETTI gait	9.2 ± 1.1*;§§	7.5 ± 1.2 §§	2.2 ± 1.1
TINETTI tot.score	21.2 ± 1.2*;§§	16.38 ± 1.3 §§	8.4 ± 1.2

* p<0.05 vs 30-45; ** p<0.01 vs 30-45; ns not significant
§p<0.05 vs 45-65; §§ p<0.01 45-65; ns not significant

complete score; a slight significant difference comes evident in Tinetti gait, equilibrium and total score. The second subitem comprises a statistical significance (p<0.001) in all the scores.

The third subitem comprises the following results: MMSE average scores, phonological and semantic fluency, mental calculation, analogies, digit backwards, apathy were worse

(mean MH statistics 458,00± 3.46; 663,00± 5.47; 562,00± 3.107; 633,00± 2.1; 756,00± 2.56, 896,00± 1.36, 1126,00± 12.6 , respectively, p<0.001). BEHAVE and digit forward were not significantly worse. Tinetti gait and equilibrium were worse (mean MH statistics 658,00± 3.46; 867,00± 5.47; 656,00± 3.107; 633,00± 2.1; 756,00± 2.56, 896,00± 1.36, 1126,00± 12.6 , respectively, p<0.001). 12 patients who received oral chemotherapy and average dosage of 45-65 Gy manifested gradually onset gait apraxia, severe enough to prevent ambulation, and urinary incontinence, with total loss of insight and awareness, and were bed-ridden at the end of the follow-up.

DISCUSSION

Our study demonstrated that there is a significant global effect of radiation on the brain; either on tumor survival either on global function decline. These effects have a time dependent course, severely related to the total radiation dose, even if we have not determined the size tumor/radiation field ratio (Valk *et al*., 1991). All the patients with a total radiation does <35 cGy did not show any sign of cognitive impairment, apart from those determined by the tumor and by the surgical consequence. On the other hand, all the patients with a total irradiation dose < 45 cGy did show profound cognitive and behavioural alteration, more evident than those manifested by a matched group of patients suffering from subcortical vascular dementia from more than 12 months. The patients who received a total dose of brain radiation comprised between 35-45 cGy did show slowness of executive functions, and profound alterations of frontal functions, such as attention focusing, mentation control, analogical judgement and insight; all the scores obtained in specific tasks did not differ from those obtained by the patients suffering from subcortical vascular dementia. Moreover, all the patients presented overt apathy and evident alterations, much more significant in those receiving more than 30 Gy or total radiation, on gait and balance. The modality of altered impairment is very similar to that seen and described in sVAD: very dramatically demonstrated by executive dysfunctions,apathy, gait alterations, and disequilibrium. What it has been observed in our study is that higher dosage of RT dramatically involved brain subcortical networks, even distant from the tumor location with a significant worsening, more rapid than the normally presented by sVAD patients.

Data from literature have been investigate, showing that older age was associated with poorer performances on all cognitive measures (Vigliani *et al*., 1996), with better performances in individuals with more education and younger, in our study brain radiated injury was directly related to the volume of brain treated with radiotherapy, not with age (lower in our group) and not with educational level (higher in our group). Our hypothesis to explain cognitive disruption due to RT may be evoked by the severe impairment of the cortical-subcortical frontal loops, which integrate and process the flow of information from the cortical areas, where cognition is "elaborated" and prepared, towards the thalamus, subthalamus and cerebellum, where it is continuously refined and executed (Metha, 2000; Hoang-Xuan *et al*., 1997). Therefore, it might be concluded that subcortical lesions, per se, cause imbalance and gait alteration: we might hypothesize that these subcortical hypoperfusion might interrupt long loop reflexes of deep white motor tracts and descending motor fibres arising from medial cortical areas, probably related to SVZ cells alterations (see data and literature in: Guerini *et al*., 2008; Moretti *et al*., 2009: Monje *et al*., 2012); moreover, subcortical vascular lesions interest fibres connecting frontal cortex and subcortical structures, which are responsible for motivation, executive function, planning and attention too (see in particular frontal eye fields). It has been suggested (see data and Literature in Moretti *et al*., 2009; Monje *et al*., 2012) that the basal ganglia maintains cortically selected motor set in the supplementary motor area and provides internal cues to the supplementary motor area in order to enable each sub movement to be correctly linked together (Iansek *et al*. 1995; Lee *et al*., 1999; Almeida *et al*., 2005; Gurvich *et al*., 2007). Cerebral atrophy with diffuse demyelination and spongiform changes in the white matter are seen pathologically (Posner, 1995).

This typical disposition make clear of the cognitive and behavioural subcortical frontal and white matter alterations, observed in our patients. Starting from the perspective that the neurocognitive sequelae of cranial irradiation can be seen to be mediated through vascular injury, resulting in ischemia and hypoxia in subcortical areas and in the hippocampal region, and that pathologic changes are most profound in the white matter where a heterogeneous necrosis can be encountered, we compared the results produced by a group of patients treated by radiotherapy and those similar to those manifested by patients suffering from subcortical vascular dementia (see data and literature in Vinai *et al*., 2010). The number of cancer survivors is still growing and long term complications after cancer treatment are becoming a serious problem for the society. However, radiotherapy might be indispensable for a "quoadvitam" discrete prognosis in specific and well selected cases, but it can be a potential causative factor of evident cognitive disruption. Consequent problems for a "quoadvaletudinem" prognosis, especially in young patients, with low-grade, late-progressing brain tumours must be taken into account, when considering the personal flow chart after the diagnosis of brain tumors. Treatment of cognitive sequelae after cerebral radiation remains very limited, more understanding about the underlying pathophysiology of RT induced vasculopathy is needed to develop preventive strategies (Brown *et al*., 2013).

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