Original Research Article

Examining the Inter Hemispheric Transfer Time Test: A new computerized cognitive test to incorporate into therapeutic strategy for patients with brain metastases? A pilot study

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ABSTRACT

Objective: To evaluate the computerized Inter Hemispheric Transfer Time Test (IHTTT), a cognitive test designed for the detection of information processing speed impairment in patients undergoing stereotactic radiation therapy for brain metastases.

Methods: Inclusion criteria: age ≥ 18 years, brain metastases treated by stereotactic radiotherapy (SRT) with dose schedule: 33 Gy in 3 fractions, solid tumour, ≥ 70 Karnofsky Performance Status, Mini-Mental State Evaluation (MMSE) ≥ 24, no history of stroke brain injury. Twenty-nine patients were recruited from June 2014 to April 2015. All recruited patients were administered Frontal Assessment Battery at Bedside (FAB), IHTTT and QLQ-C30 quality of life questionnaire before SRT, at one-month, six-month and one-year follow-up. The primary endpoint was Interhemispheric Transfer Index (IHTI). Secondary endpoints included Interhemispheric Transfer Time (IHTT), MMSE, FAB, and quality of life.

Results: A significant evolution of cognitive function over time was assessed by the IHTTT: IHTT = 720 ± 27 ms at baseline, 728 ± 20 at one month, 736 ± 36 at 6 months, 799 ± 111 at one-year follow-up (p = 0.0010); IHTI = 13.1 ± 31.4, 11.5 ± 24.3, 50.6 ± 57.9, 91.0 ± 59.4 (p < 0.0001). There was also a significant evolution over time for MMSE (p = 0.014) but neither for FAB score nor the quality of life scores. IHTI was strongly related to progression-free survival (p = 0.0091).

Conclusion: Our results suggest that IHTTT is able to detect the evolution of cognitive function over time. IHTTT could be an interesting sensitive cognitive test to include in evaluation of patients with brain metastases irradiated by SRT.

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1. Introduction

Historically, whole brain radiotherapy (WBRT) was the standard treatment for multiple brain metastases. Its benefit in terms of improved tumor control and overall survival is well demonstrated [1–3]. For one to four brain metastases, stereotactic radiotherapy has become a new standard for patients with a good prognostic score to preserve cognitive functions by sparing a part of the brain from brain irradiation [4]. Stereotactic Radiotherapy (SRT) does not improve overall survival compared to WBRT [3,5,6].

More and more studies have been conducted, including cognitive tests in patients with brain malignancies. In fact, neurocognitive status could have a predictive and prognostic value in this population and be of considerable help in choice of therapeutic strategy [7]. Neurocognitive assessment must be brief and sensitive in this asthenic population. The most impaired brain-based cognitive skills after radiation therapy in patients with brain metastases are the executive functions [8,9].

That is why we decided to choose the InterHemispheric Transfer Time Test (IHTTT) as a cognitive evaluation tool, which detects information processing speed impairment. It is short (10 min), repeatable, simple to administer but not standardized. In this prospective study, we share our initial experience using this computerized cognitive test for detection of information processing speed impairment in patients undergoing stereotactic radiotherapy for brain metastases.

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The aim of this pilot observational study was to evaluate computerized IHTTT for the detection of information processing speed impairment in patients with radiation therapy for brain metastases.

2. Material and methods

2.1. Patients and study design

Eligibility criteria were as follows: patients (M/F) aged over 18 years, with one to four brain metastases treated by SRT with dose schedule: 33 Gy in 3 fractions, with a solid tumour, ≥70 Karnofsky Performance Status, Mini-Mental State Evaluation (MMSE) ≥ 24, without psychiatric disorder, without recent medical history of stroke brain injury, without visual disorders (blindness or diplopia) and a right hand preference. Exclusion criteria were as follows: <70 Karnofsky Performance Status, carcinoma meningitis, chemotherapy concomitant with radiation therapy, medical history of radiation therapy, upper limb paralysis, recent medical history of stroke (ischemic) brain injury. This pilot study was designed as prospective, longitudinal and transversal, non-comparative including currently treated patient without any therapeutic intervention and without untreated control group. This exploratory study aimed to evaluate pertinence and potential clinical utility of the IHTT.

Twenty-nine patients were recruited in our center from June 2014 through April 2015. All recruited patients were administered a Mini-Mental State Evaluation (MMSE), the Frontal Assessment Battery at Bedside (FAB), the computerized IHTTT and the QLQ-C30 quality of life questionnaire before SRT (at baseline), and at one month, six month and one year follow-up. Cognitive assessments were conducted by the main author or by medical students under her supervision. Each patient underwent whole-body CT scan and brain MRI to determine intracranial and extra-cranial status at 6 month and at one-year follow-up.

All patients were informed about the study and that their test results would have no impact on their treatment plan. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients gave written informed consent.

2.2. Radiotherapy

Each patient received SRT. The SRT dosage schedule was 33 Gy in 3 fractions over one week. Adequate target coverage was achieved when 100% of the Planning Target Volume (PTV) was covered by isodose 70%. This hypo-fractionated radiotherapy was carried out with a 6 MV linear accelerator (Clinac 600) with a micro multileaf collimator M3 (Brainlab®) with a leaf width of 3 mm at isocenter.

Radiotherapy planning was based on computed tomography (CT) fusioned with MRI with 2 mm and 0.8 mm slice thickness respectively. Patients were immobilized in a thermoplastic mask. Treatment planning was performed with iPlan RT Image 4.1.1 (BrainLab, Feld-kirchen/Germany). Gross Tumor Volume was delineated on the GdT1-MRI. The PTV was defined as Clinical Target Volume (CTV) expanded with a 2 mm margin.

2.3. Cognitive assessments

Mini Mental Status Exam (MMSE) is a brief and widely used 30-point screening test developed for assessment of cognitive impairment. It evaluates arithmetical, memory and orientation domains It is important to administer it in complementarity with neuropsychological tests [10,11].

Frontal Assessment Battery (FAB) has been developed for the assessment of executive functions. It lasts 10 min. It consists of six subtests. Each subtest is scored on a maximum of 3 points, rendering a total maximum score of 18 [12].

2.4. IHTT test

IHTT test is based on Poffenberger paradigm created to estimate the time required for the critical transfer of information from one hemisphere to other [13].

During this test, the patient was seated in front of a computer with a joystick in his hands and instructed to look at the middle of the screen. Stimuli were arrows appearing tachistoscopically (250 ms) on the right or on the left and pointing to the right or to the left. The visual information was treated selectively by the hemisphere opposite to stimulation. The patient should click right when the arrow indicated right and left when the arrow indicated left. If the arrow appeared to the right and indicated the right or if the arrow appeared to the left and indicated the left, the situation was congruent. Visual information was perceived in ipsilateral hemisphere, which controls motor control and therefore does not have to pass through the corpus callosum (which is the connective structure between the two cerebral hemispheres). Intrahemispheric transfer was evaluated (additional material). If the arrow appeared to the right and indicated the left or if the arrow appeared to the left and indicated the right, the situation was incongruent. The visual information is perceived in the hemisphere contralateral to the motor control and must therefore pass through the corpus callosum. Inter-hemispheric transfer was evaluated (additional material) [14]. Lesions of the white matter are indeed responsible for non-specific cognitive disorders (slowed processing speed, difficulties in multiple tasks) revealed by a deficit of the executive functions [8,15]. The objective of this test was to sensitize evaluation of the executive functions by measurement of reaction time and comparison of intra- and interhemispheric transfer times during an inhibitor control task (Stroop test). Several variables were measured:

1-The reaction time (IHTT) between presentation of the visual stimulus and the response obtained by the joystick.

2-The inter-hemispheric transfer index (IHTI), which corresponds to the delta of the response time between the incongruent and congruent situations because transfer of the information over the corpus callosum results in a time delay.

The hypothesis was that IHTT and IHTI are more sensitive measures than MMSE or FAB to evaluate executive functions in post-radiation lesions.

2.5. Quality of life assessment (QLQ C30)

EORTC QLQ-C30 is a specific tool assessing the quality of life of cancer patients is the most widely used test in clinical trials Four scores were calculated using the EORTC scoring procedures (rendering a score ranging from 0 to 100): global health status; functional scale; symptom scale; cognitive functioning [16].

2.6. Statistical analysis

IHTI measurement was the primary endpoint. Secondary endpoints included IHTT measurement, MMSE score, FAB score, quality of life scores, prognostic scores: recursive partitioning analysis (RPA) and graded prognostic assessment (GPA), progression-free survival (PFS, calculated from the date of the end of brain radiation therapy to the date of the first imaging showing cerebral progression) and overall survival (OS).

Descriptive statistics (mean and, standard deviation, or number and percent) were used to report data. Evolution of endpoints was analyzed by mixed linear models for repeated measures, taking into account the longitudinal design with incomplete observations over time. Non-independences resulting from serial observations belonging to the same individual were accounted by a first-order autoregressive correlation structure. Deviations from distribution hypothesis were assessed on the residuals computed after fitting the models. Correlation analysis between IHTI, IHTT, GPA, MMSE, FAB, and QLQ-C30 scores was performed using the non-parametric Spearman correlation coefficient. PFS and OS analyses used the Kaplan–Meier method. The univariate survival analysis used the log-rank test. Multivariate survival analyses were performed using the Cox proportional hazards model with variables entering the model following a forward-stepwise selection procedure. For each test, a p-value ≤ 0.05 was considered statistically significant. Statistical analysis was carried out using SAS version 9.4 (SAS institute, Cary, NC).

3. Results

Thirty-three patients were eligible for stereotactic radiotherapy. Four patients were not included due to application of non-inclusion criteria. Twenty-nine patients were included from June 2014 through April 2015. At 6-month follow-up, 1 patient was excluded due to cerebral progression and two other patients at one-year follow-up. The cognitive test results of 26 patients in the stereotactic group were then analyzed (Fig. 1). At baseline, 43% of patients received corticosteroids and 36% anti-epileptic drugs against 0% respectively at one year. The most frequent primary tumor site was lung (58%). Patient characteristics are represented in Table 1.

At baseline, IHTI and IHTT were respectively 131.0 ± 31.4 ms and 720.3 ± 26.5. IHTI and IHTT showed significant evolution over time after stereotactic radiotherapy (p = 0.0001 and p = 0.0010, respectively). IHTI and IHTT were stable at one month and then worsened over time (Fig. 2).

Preceding SRT, patients had no impairment regarding MMSE and FAB results with 29.5 ± 0.7 points and 17.4 ± 1.1 respectively. MMSE scores were significantly worse at one-year follow-up compared with baseline, one month and 6 month follow up (p = 0.014). FAB showed a non-significant trend toward impairment at one-year follow-up (p = 0.13). IHTT was correlated with the MMSE (Spearman $r_S = -0.56$) and the FAB ($r_S = -0,68$). The use of corticosteroids, RPA scores, brain metastasis surgery, sex, number of brain metastases and their volume were not associated with neurocognitive functioning (data not shown).

Compared with the general population, quality-of-life QLQ-C30 scores were similar in patients at baseline for global health status, global functional scales and cognitive functioning (76,2 ± 18,9 versus 78 for general population, 85,2 ± 15,4 versus 90, 86.2 ± 23.3 versus 92 respectively) [17]. Despite a decreasing quality of life of patients over time, this evolution was not statistically significant (Table 2). There was no correlation between IHTTT scores and QLQ-C30 scores (Table 3). The use of corticosteroids, RPA scores, brain metastasis surgery, number of brain metastases and their volume were not associated with quality of life (data not shown).

Median OS was 15 months and median PFS 8,75 months (Fig. 3); 57% of patients died due to cerebral progression. Univariate logrank test showed that low IHTI was significantly associated with better PFS (p = 0.0091). Moreover, GPA was moderately asso-
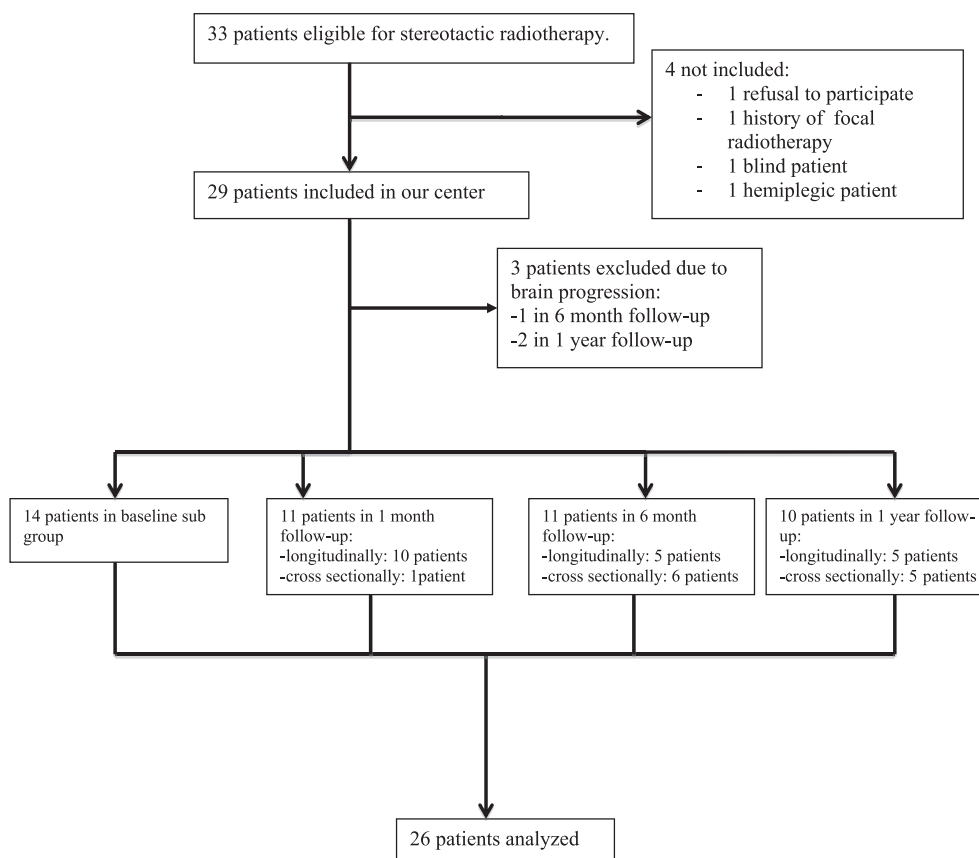

Fig. 1. Flow chart.

Table 1
Baseline characteristics of the patients.

	Baseline	1 month	6 months	1 year
Patients (N)	14	11	11	10
Age (y)				
Median (min–max)	58 (36–71)	60 (36–71)	61 (45–71)	62 (51–81)
Mean ± sd	56 ± 10	58 ± 11	60 ± 7	65 ± 10
Sex (N, %)				
Men	8 (57)	5 (45)	6 (55)	7 (70)
Women	6 (43)	6 (55)	5 (45)	3 (30)
Brain metastases (N, %)				
1–3	14 (1 0 0)	11 (1 0 0)	12 (1 0 0)	9 (90)
>3	0	0	0	1 (10)
Metastases undergoing surgery (N, %)	5 (36)	4 (36)	2 (18)	4 (40)
RPA				
1	4 (29)	3 (27)	6 (55)	4 (40)
2	10 (71)	8 (73)	5 (45)	6 (60)
3	0	0	0	0
GPA (N, %)				
0–1	0	0	0	1 (10)
1,5–2,5	8 (57)	7 (64)	6 (55)	4 (40)
3	2 (14)	2 (18)	2 (18)	2 (20)
3,5–4	4 (29)	2 (18)	3 (27)	3 (30)
Primary tumor (N, %)				
Lung	9 (64)	5 (46)	6 (55)	4 (40)
Breast	2 (14)	2 (18)	1 (9)	0
Kidney	0	0	1 (9)	3 (30)
Melanoma	2 (14)	2 (18)	1 (9)	3 (30)
Other	1 (7)	2 (18)	2 (18)	0
Metastasis diameter (N, %)				
≥3 cm	5 (36)	4 (36)	1(9)	3 (30)
<3 cm	9 (64)	7 (64)	10 (91)	7 (70)
Tumor main axis (mm)				
Mean ± sd	25 ± 16	24 ± 17	17 ± 7	24 ± 21
Median (min–max)	19 (6–60)	18 (6–60)	18 (6–30)	17 (7–61)
Education (N, %)				
< compulsory education	0	0	0	0
Compulsory education	2 (14)	1 (10)	2 (18)	4 (40)
Secondary school	6 (43)	5 (45)	6 (55)	4 (40)
Higher education	6 (43)	5 (45)	3 (27)	2 (20)
Treatments (N, %)				
Anxiolytic	1 (7)	0	3 (27)	1 (10)
Anti-depressive	0	0	1 (9)	1 (10)
Antalgic level 2 and 3	1 (7)	0	3 (27)	1 (10)
Anti-epileptic	5 (36)	4 (36)	4 (36)	0
Corticosteroids	6 (43)	6 (55)	4 (36)	1 (10)
Chemotherapy	2 (14)	8 (73)	9 (82)	5 (50)
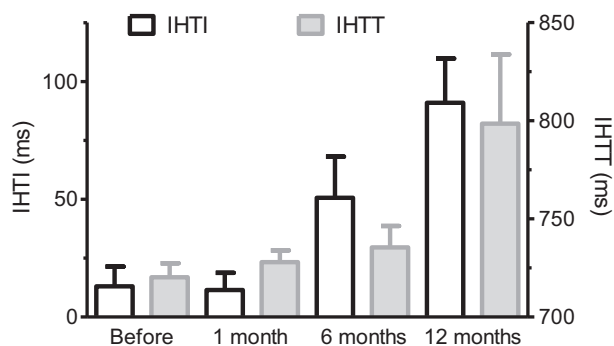
Fig. 2. Evolution of IHTT and IHTI over time (mean and sd, milliseconds).

ciated with PFS (p = 0.058). Multivariate analysis revealed that predictive factors for better PFS were low IHTI (p = 0.024) and low GPA score (p = 0.039). MMSE and FAB scores were not associated with PFS.

4. Discussion

4.1. Choice of cognitive tests

We chose IHTTT as a computerized cognitive evaluation test because of its speed of execution (10 min) and its ease to administrate. It evaluates psychomotor retardation, concentration and attention disorders. These functions are often impaired in brain radiotherapy patients [18]. This test seemed promising as a future evaluation tool, which could help us in therapeutic decision-making on the choice of radiotherapy modalities (WBRT versus stereotactic radiotherapy) or re-irradiation. But this test has yet to be standardized. That is why we added two other validated tests: the MMSE and the FAB.

The choice of MMSE as a cognitive test for irradiated patients for cerebral metastases can be criticized for its low sensitivity and specificity. Indeed, the MMSE is not a psychometric test but rather a standardized clinical examination that does not have the metrological qualities of the psychometric tests [11,19]. However, the MMSE is a good standardized tool because of its simple admin-

Table 2
Evolution with time of the cognitive tests and the quality of life scores.

	Before	1 month	6 months	1 year	P
IHTI (ms)	13.1 ± 31.4	11.5 ± 24.3	50.6 ± 57.9	91.0 ± 59.4	<0.0001
IHTT (ms)	720 ± 27	728 ± 20	736 ± 36	799 ± 111	0.0010
MMSE (/30)	29.5 ± 0.7	29.7 ± 0.7	29.4 ± 0.8	28.5 ± 1.2	0.014
FAB (/18)	17.4 ± 1.1	17.7 ± 0.5	17.7 ± 0.5	16.4 ± 1.8	0.13
QLQ-C30 (/100)					
Global health	76.2 ± 18.9	75.0 ± 16.2	64.3 ± 16.3	60.0 ± 19.6	0.15
Functional	85.2 ± 15.4	80.4 ± 19.2	71.8 ± 18.3	71.9 ± 19.1	0.10
Cognitive	86.2 ± 23.3	90.0 ± 22.6	80.5 ± 22.2	72.0 ± 28.4	0.21
Symptoms	84.5 ± 14.3	85.2 ± 11.2	79.2 ± 12.9	79.2 ± 10.3	0.86

P: p-value of the time effect estimated from mixed linear model for repeated measures.

Table 3
Correlation analysis at baseline of cognitive tests and quality of life scores.

	IHTI	IHTT	GPA
MMSE	$r_S = 0.20$	$r_S = -0.56$	$r_S = 0.41$
	$P = 0.50$	$P = 0.039$	$P = 0.15$
FAB	$r_S = -0.03$	$r_S = -0.68$	$r_S = 0.53$
	$P = 0.91$	$P = 0.0079$	$P = 0.050$
QLQ-C30			
Global health	$r_S = -0.03$	$r_S = 0.017$	$r_S = -0.22$
	$P = 0.92$	$P = 0.96$	$P = 0.46$
Functional	$r_S = -0.38$	$r_S = 0.00$	$r_S = -0.19$
	$P = 0.20$	$P = 0.99$	$P = 0.53$
Cognitive	$r_S = -0.07$	$r_S = 0.29$	$r_S = -0.15$
	$P = 0.81$	$P = 0.34$	$P = 0.63$
Symptoms	$r_S = -0.07$	$r_S = 0.11$	$r_S = -0.34$
	$P = 0.81$	$P = 0.72$	$P = 0.25$

r_S: Spearman nonparametric correlation coefficient.
P: p-value of Spearman's test of correlation.
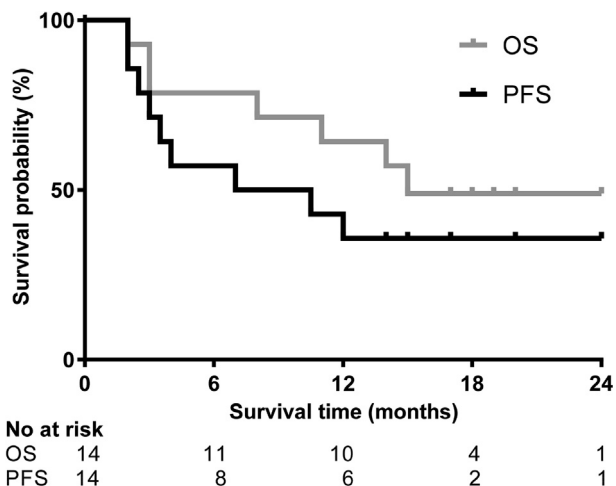
Fig. 3. Overall survival (OS) and cerebral progression-free survival (PFS, months).

istration and deserves to be included, in addition to neuropsychological tests, in the systematic examination of patients with brain lesions. It is quick to administrate in tired patients. FAB appeared to be a good complement to the MMSE because it evaluates the executive functions, which are often impaired in patients irradiated for brain metastases, something that MMSE cannot do [9].

4.2. Results comments

Our results suggest that IHTTT could be a discriminant test measuring the cognitive impact of brain radiotherapy, especially stereotactic radiotherapy. IHTT as well as IHTI evolves over time

significantly and conclusively. IHTT and IHTI are stable at one month and subsequently only worsen with time. We can suspect alteration of the white substance on the irradiated side, resulting in lengthening of the IHTT on that side only (transfer time for the information being longer) and also in IHTI lengthening. IHTTT results reflect attention disorders and psychomotor slowing induced by the rays. MMSE detects significant evolution of the cognitive functions contrary to FAB (respectively p = 0.014 and 0.13).

However, if we can detect cognitive toxicity in this population, this does not mean that radiotherapy is of no benefit to them. Indeed, the benefit of stereotactic radiotherapy in terms of its anti-tumor effect, loco-regional control and overall survival is well-established [20–22]. This is likewise reflected in our results through complete steroid anti-epileptic withdrawal and at one-year follow-up (36% of patients under anti-epileptics and 43% of patients under corticosteroids in stereotactic radiotherapy group baseline versus 0% at one-year follow up. Quality of life tends to worsen over time but the results were statistically insignificant.

Concerning the correlations between the different cognitive tests and quality of life, IHTT was significantly correlated with the MMSE and the FAB, but not with patient quality of life. Correlation between IHTTT and the FAB was not surprising because both of them evaluate the executive functions. Few studies have evaluated the changes in cognitive function following stereotactic radiotherapy for brain metastases. Concerning IHTTT, our results support the hypothesis of radiation-induced lesions of the white matter. Stokes' TB study supports our results [8]. Indeed, the authors compared changes in white matter on T2-weighted and FLAIR-weighted cerebral MRI in patients with brain-metastatic breast cancer. One group received stereotaxy alone (n = 30) and the other received WBRT associated with cerebral stereotaxy (n = 35). Patients had cerebral MRI at baseline and then at one-year follow-up. At one-year follow-up, the stereotactic + WBRT group showed a high incidence of changes in white matter (71.5%, p < 0.05) versus only 3.3% in the stereotactic group. The study by Monaco and al. confirms these findings in patients with brain metastatic lung cancer [15]. According to Hulst and al., lesions of the white matter are correlated with the deterioration of cognitive functions [23]. Our study finds significant aggravation of the cognitive functions: +78 ms for the index and IHTT between baseline and one year follow-up.

Dane and al [24] demonstrated that reaction times were longer in women than in men and that left handed players have probably an intrinsic neurological advantage. Controlling theses variables should not change our results because our patients had a right hand preference and groups were comparable.

Moreover, patient quality of life after neuro-radio-induced toxicity requires close evaluation and analysis. Indeed, in patients with cerebral metastases, neurocognitive functions and activities of daily life (QoL) could be correlated. A decline in neurocognitive functions would be predictive of a decline in the QoL score [25].

Our study does not find this correlation because IHTTT investigate a relatively narrow aspect of cognitive performance.

The median OS of 15 months for RPA Class I and II was longer than the value predicted in the original paper by Gaspar et al. (7.1 vs. 4.2 for Class I and II respectively) [26]. This can be explained by the fact that patients have fewer than 5 brain metastases and that 30% of patients underwent surgery for their brain metastases. Median OS after resection of brain metastasis is differently reported in literature in a range between 6 and 17 months [27]. The most frequently used scoring systems to predict the outcome are RPA and GPA [28]. In our study, IHTI seems to be an independent factor for prediction of brain PFS. Being more accurate than RPA and GPA in our study, it could be incorporated into therapeutic decision-making.

4.3. Study limits

The study was not optimally designed. Indeed, our study was not a true longitudinal study. We were unable to monitor each patient over time because many of them died prematurely or rapidly deteriorated, preventing any cognitive test. Other patients left the study at their request because of displacement-related fatigue when they lived far away. To compensate for the large number of patients who left the study early, we chose to include patients cross-sectionally at 6 months and at one-year follow-up to increase our enrollment. Our study was therefore both longitudinal and transversal. We consequently evaluated evolution of the cognitive functions over time in patients who were not always the same, thereby exposing to selection bias. But group characteristics were comparable.

4.4. Perspectives

To preserve cognitive functions in patients irradiated on the brain, drugs could be efficient. A phase III study (RTOG 0614) studied memantine for the prevention of radio-induced cognitive toxicity. Memantine is a drug blocking anti-methyl aspartate receptor that has been shown to be effective in Alzheimer disease. In this study 508 patients with cerebral metastases were randomized between complete brain irradiation with memantine for 6 months, and complete brain irradiation with a placebo for 6 months. Patients in the memantine group had a probability of cognitive decline at 6 months of 54% versus 65% in the placebo group (HR = 0.78, p = 0.01 [29]. At present, an on-going randomized phase III trial is comparing memantine hydrochloride and whole-brain radiotherapy with or without hippocampal avoidance as a means of reducing neurocognitive decline in patients with cancer that has spread from the primary site to the brain (NCT02360215)

Moreover, the impairment of cognitive functions in patients irradiated on the brain raises questions on the possible efficacy of cognitive rehabilitation. The study of Gehring et al. studied the cognitive impact of cognitive rehabilitation programs in brain tumor patients. A group of patients with brain tumor utilized from a computerized program of attention training and learning of cognitive impairment rehabilitation techniques for 6 weeks. Another group of control patients did not yet benefit from the cognitive Rehabilitation Program (waiting list). Patients who had utilized the cognitive rehabilitation program presented significantly better results in neuropsychological tests at 6 months compared with the control group [30]. Kesler et al. found a beneficial effect of a computerized cognitive re-education program on executive functions, verbal fluency and information-processing speed [31]. On account of brain plasticity, cognitive rehabilitation should be interesting in this population. A clinical trial is currently recruiting participants to assess the Impact of Cognitive Rehabilitation and Physical Activity on Cognition in Patients with Metastatic Brain Tumors Undergoing RT (NCT03096431).

Finally, a treatment adapted to each patient is necessary. We should neither over-treat patients with negative prognosis nor treat those with favorable prognosis (long-term adverse effects). Taking a rapid cognitive test (which is feasible, for example, during consultation with a radiotherapist) before deciding on cerebral therapeutic strategy could be a better way of selecting patients. The test seems predictive of brain progression-free survival and could be incorporated into therapeutic decision-making.

5. Conclusion

This prospective pilot study suggests the interest of IHTTT in therapeutic management.

The IHTT test would be a discriminatory test to assess cognitive function in evaluation of patients with brain metastases irradiated by SRT. The IHTTT could become an assessment tool to be considered as a new element in a therapeutic strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2018.11.006.

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