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1 **Title Page**

2

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

6

7 Authors: Emmanuelle REYGAGNE^a, Foucaud DU BOISGUEHENEUC^b, Antoine
8 BERGER^a, Pierre INGRAND^{c,d}

9 ^a Radiotherapy department, CHU Poitiers, France *emmanuelle.reygagne@hotmail.fr*

10 ^b Neurology department, CHU Poitiers, France *foucaud.duboisgueheneuc@chu-poitiers.fr*

11 ^a INSERM CIC 1402, CHU, Poitiers, France *antoine.berger@chu-poitiers.fr*

12 ^{c,d} Epidemiology and Biostatistics, Poitou-Charentes cancer registry, University of
13 Poitiers, France *pierre.ingrand@univ-poitiers.fr*

14

15 Running title: Cognition and stereotactic brain radiotherapy: a pilot study.

16 Corresponding author: Emmanuelle REYGAGNE. CHU de Poitiers. 2, rue de la Milétrie.
17 86000 Poitiers, France. Phone number +33 6 19 20 78 65. Email:
18 *emmanuelle.reygagne@hotmail.fr*

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22

23 **ABSTRACT**

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

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

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

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

44

45 **Keywords:** stereotactic, radiation therapy, brain metastases, cognitive test

46

47 **Introduction**

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

54 More and more studies have been conducted, including cognitive tests in patients with brain
55 malignancies. In fact, neurocognitive status could have a predictive and prognostic value in
56 this population and be of considerable help in choice of therapeutic strategy [7].

57 Neurocognitive assessment must be brief and sensitive in this asthenic population. The most
58 impaired brain-based cognitive skills after radiation therapy in patients with brain metastases
59 are the executive functions [8,9].

60 That is why we decided to choose the InterHemispheric Transfer Time Test (IHTTT) as a
61 cognitive evaluation tool, which detects information processing speed impairment. It is short
62 (10 minutes), repeatable, simple to administer but not standardized. In this prospective study,
63 we share our initial experience using this computerized cognitive test for detection of
64 information processing speed impairment in patients undergoing stereotactic radiotherapy for
65 brain metastases.

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

69

70 **Material and methods**

71 *Patients and study design*

72 Eligibility criteria were as follows: patients (M/F) aged over 18 years, with one to four brain
73 metastases treated by SRT with dose schedule: 33 Gy in 3 fractions, with a solid tumour, ≥ 70
74 Karnofsky Performance Status, Mini-Mental State Evaluation (MMSE) ≥ 24 , without
75 psychiatric disorder, without recent medical history of stroke brain injury, without visual
76 disorders (blindness or diplopia) and a right hand preference. Exclusion criteria were as
77 follows: < 70 Karnofsky Performance Status, carcinoma meningitis, chemotherapy
78 concomitant with radiation therapy, medical history of radiation therapy, upper limb paralysis,
79 recent medical history of stroke (ischemic) brain injury. This pilot study was designed as
80 prospective, longitudinal and transversal, non-comparative including currently treated
81 patient without any therapeutic intervention and without untreated control group.. This
82 exploratory study aimed to evaluate pertinence and potential clinical utility of the IHTT.
83 Twenty-nine patients were recruited in our center from June 2014 through April 2015. All
84 recruited patients were administered a Mini-Mental State Evaluation (MMSE), the Frontal
85 Assessment Battery at Bedside (FAB), the computerized IHTTT and the QLQ-C30 quality of
86 life questionnaire before SRT (at baseline), and at one month, six month and one year follow-
87 up. Cognitive assessments were conducted by the main author or by medical students under
88 her supervision. Each patient underwent whole-body CT scan and brain MRI to determine
89 intracranial and extra-cranial status at 6 month and at one-year follow-up.
90 All patients were informed about the study and that their test results would have no impact on
91 their treatment plan. All procedures performed in this study were in accordance with the
92 ethical standards of the institutional research committee and with the 1964 Helsinki
93 declaration and its later amendments or comparable ethical standards. All patients gave
94 written informed consent.

95

96 *Radiotherapy*

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

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

107

108 *Cognitive assessments*

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

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

116

117 IHTT Test.

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

120 During this test, the patient was seated in front of a computer with a joystick in his hands and
121 instructed to look at the middle of the screen. Stimuli were arrows appearing tachitoscopically
122 (250 ms) on the right or on the left and pointing to the right or to the left. The visual
123 information was treated ~~exclusively~~ selectively by the hemisphere opposite to stimulation.
124 The patient should click right when the arrow indicated right and left when the arrow
125 indicated left. If the arrow appeared to the right and indicated the right or if the arrow
126 appeared to the left and indicated the left, the situation was congruent. Visual information was
127 perceived in ~~level of the~~ ipsilateral hemisphere, which controls motor control and therefore
128 does not have to pass through the corpus callosum (which is the connective structure between
129 the two cerebral hemispheres). Intra-hemispheric transfer was evaluated (additional material).
130 If the arrow appeared to the right and indicated the left or if the arrow appeared to the left and
131 indicated the right, the situation was incongruent. The visual information is perceived in the
132 hemisphere contralateral to the motor control and must therefore pass through the corpus
133 callosum. Inter-hemispheric transfer was evaluated (additional material) [14]. Lesions of the
134 white matter are indeed responsible for non-specific cognitive disorders (slowed processing
135 speed, difficulties in multiple tasks) revealed by a deficit of the executive functions [8,15].
136 The objective of this test was to sensitize evaluation of the executive functions by
137 measurement of reaction time and comparison of intra- and interhemispheric transfer times
138 during an inhibitor control task (Stroop test). Several variables were measured:
139 1-The reaction time (IHTT) between presentation of the visual stimulus and the response
140 obtained by the joystick.
141 2-The inter-hemispheric transfer index (IHTI), which corresponds to the delta of the response
142 time between the incongruent and congruent situations because transfer of the information
143 over the corpus callosum results in a time delay.

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

146

147 *Quality of life assessment (QLQ C30)*

148

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

153

154

155

156 *Statistical Analysis*

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

162 Descriptive statistics (mean and, standard deviation, or number and percent) were used to
163 report data. Evolution of endpoints was analyzed by mixed linear models for repeated
164 measures, taking into account the longitudinal design with incomplete observations over time.

165 Non-independences resulting from serial observations belonging to the same individual were
166 accounted by a first-order autoregressive correlation structure. Deviations from distribution

167 hypothesis were assessed on the residuals computed after fitting the models. Correlation

168 analysis between IHTI, IHTT, GPA, MMSE, FAB, and QLQ-C30 scores was performed

169 using the non-parametric Spearman correlation coefficient. PFS and OS analyses used the
170 Kaplan–Meier method. The univariate survival analysis used the log-rank test. Multivariate
171 survival analyses were performed using the Cox proportional hazards model with variables
172 entering the model following a forward-stepwise selection procedure. For each test, a p-value
173 ≤ 0.05 was considered statistically significant. Statistical analysis was carried out using SAS
174 version 9.4 (SAS institute, Cary, NC).

175

176 **Results**

177 Thirty-three patients were eligible for stereotactic radiotherapy. Four patients were not
178 included due to application of non-inclusion criteria. Twenty-nine patients were included
179 from June 2014 through April 2015. At 6-month follow-up, 1 patient was excluded due to
180 cerebral progression and two other patients at one-year follow-up. The cognitive test results of
181 26 patients in the stereotactic group were then analyzed (Figure 1). At baseline, 43% of
182 patients received corticosteroids and 36% anti-epileptic drugs against 0% respectively at one
183 year. The most frequent primary tumor site was lung (58%). Patient characteristics are
184 represented in table 1.

185 *Table 1 and Figure 1 approximately here*

186

187 At baseline, IHTI and IHTT were respectively 131.0 ± 31.4 ms and 720.3 ± 26.5 . IHTI and
188 IHTT showed significant evolution over time after stereotactic radiotherapy ($p=0.0001$ and
189 $p=0.0010$, respectively). IHTI and IHTT were stable at one month and then worsened over
190 time (Figure 2).

191 *Figure 2 approximately here*

192 Preceding SRT, patients had no impairment regarding MMSE and FAB results with $29.5 \pm$
193 0.7 points and 17.4 ± 1.1 respectively. MMSE scores were significantly worse at one-year

194 follow-up compared with baseline, one month and 6 month follow up ($p=0.014$). FAB showed
195 a non-significant trend toward impairment at one-year follow-up ($p=0.13$). IHTT was
196 correlated with the MMSE (Spearman $r_s=-0.56$) and the FAB ($r_s=-0,68$). The use of
197 corticosteroids, RPA scores, brain metastasis surgery, sex, number of brain metastases and
198 their volume were not associated with neurocognitive functioning (data not shown).
199 Compared with the general population, quality-of-life QLQ-C30 scores were similar in
200 patients at baseline for global health status, global functional scales and cognitive functioning
201 ($76,2 \pm 18,9$ versus 78 for general population, $85,2 \pm 15,4$ versus 90, 86.2 ± 23.3 versus 92
202 respectively) [17]. Despite a decreasing quality of life of patients over time, this evolution
203 was not statistically significant (Table 2). There was no correlation between IHTTT scores
204 and QLQ-C30 scores (Table 3). The use of corticosteroids, RPA scores, brain metastasis
205 surgery, number of brain metastases and their volume were not associated with quality of life
206 (data not shown).

207 *Tables 2 and 3, and Figure 3 approximately here*

208 Median OS was 15 months and median PFS 8,75 months (Figure III); 57% of patients died
209 due to cerebral progression. Univariate logrank test showed that low IHTI was significantly
210 associated with better PFS ($p=0.0091$). Moreover, GPA was moderately associated with PFS
211 ($p= 0.058$). Multivariate analysis revealed that predictive factors for better PFS were low
212 IHTI ($p=0.024$) and low GPA score ($p=0.039$). MMSE and FAB scores were not associated
213 with PFS.

214

215 **Discussion**

216 *Choice of cognitive tests*

217 We chose IHTTT as a computerized cognitive evaluation test because of its speed of
218 execution (10 minutes) and its ease to administrate. It evaluates psychomotor retardation,
219 concentration and attention disorders. These functions are often impaired in brain
220 radiotherapy patients [18]. This test seemed promising as a future evaluation tool, which
221 could help us in therapeutic decision-making on the choice of radiotherapy modalities
222 (WBRT versus stereotactic radiotherapy) or re-irradiation. But this test has yet to be
223 standardized. That is why we added two other validated tests: the MMSE and the FAB.
224 The choice of MMSE as a cognitive test for irradiated patients for cerebral metastases can be
225 criticized for its low sensitivity and specificity. Indeed, the MMSE is not a psychometric test
226 but rather a standardized clinical examination that does not have the metrological qualities of
227 the psychometric tests [11,19]. However, the MMSE is a good standardized tool because of its
228 simple administration and deserves to be included, in addition to neuropsychological tests, in
229 the systematic examination of patients with brain lesions. It is quick to administrate in tired
230 patients. FAB appeared to be a good complement to the MMSE because it evaluates the
231 executive functions, which are often impaired in patients irradiated for brain metastases,
232 something that MMSE cannot do [9].

233

234 Results comments

235 Our results suggest that IHTTT could be a discriminant test measuring the cognitive impact of
236 brain radiotherapy, especially stereotactic radiotherapy. IHTT as well as IHTI evolves over
237 time significantly and conclusively. IHTT and IHTI are stable at one month and subsequently
238 only worsen with time. We can suspect alteration of the white substance on the irradiated side,
239 resulting in lengthening of the IHTT on that side only (transfer time for the information being
240 longer) and also in IHTI lengthening. IHTTT results reflect attention disorders and

241 psychomotor slowing induced by the rays. MMSE detects significant evolution of the
242 cognitive functions contrary to FAB (respectively $p = 0.014$ and 0.13).

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

250 Concerning the correlations between the different cognitive tests and quality of life, IHTT
251 was significantly correlated with the MMSE and the FAB, but not with patient quality of life.
252 Correlation between IHTTT and the FAB was not surprising because both of them evaluate
253 the executive functions. Few studies have evaluated the changes in cognitive function
254 following stereotactic radiotherapy for brain metastases. Concerning IHTTT, our results
255 support the hypothesis of radiation-induced lesions of the white matter. Stokes' TB study
256 supports our results [8]. Indeed, the authors compared changes in white matter on T2-
257 weighted and FLAIR-weighted cerebral MRI in patients with brain-metastatic breast cancer.
258 One group received stereotaxy alone ($n = 30$) and the other received WBRT associated with
259 cerebral stereotaxy ($n = 35$). Patients had cerebral MRI at baseline and then at one-year
260 follow-up. At one-year follow-up, the stereotactic + WBRT group showed a high incidence of
261 changes in white matter (71.5%, $p < 0.05$) versus only 3.3% in the stereotactic group. The
262 study by Monaco and al. confirms these findings in patients with brain metastatic lung cancer
263 [15]. According to Hulst and al., lesions of the white matter are correlated with the
264 deterioration of cognitive functions [23]. Our study finds significant aggravation of the
265 cognitive functions: +78 ms for the index and IHTT between baseline and one year follow-up.

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

270 Moreover, patient quality of life after neuro-radio-induced toxicity requires close evaluation
271 and analysis. Indeed, in patients with cerebral metastases, neurocognitive functions and
272 activities of daily life (QoL) could be correlated. A decline in neurocognitive functions would
273 be predictive of a decline in the QoL score [25]. Our study does not find this correlation
274 ~~between cognitive functions and quality of life~~ because IHTTT investigate a relatively narrow
275 aspect of cognitive performance .

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

285

286 *Study limits*

287 The study was not optimally designed. Indeed, our study was not a true longitudinal study.
288 We were unable to monitor each patient over time because many of them died prematurely or
289 rapidly deteriorated, preventing any cognitive test. Other patients left the study at their request
290 because of displacement-related fatigue when they lived far away. To compensate for the

291 large number of patients who left the study early, we chose to include patients cross-
292 sectionally at 6 months and at one-year follow-up to increase our enrollment. Our study was
293 therefore both longitudinal and transversal. We consequently evaluated evolution of the
294 cognitive functions over time in patients who were not always the same, thereby exposing to
295 selection bias. But group characteristics were comparable.

296

297 *Perspectives*

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

309 Moreover, the impairment of cognitive functions in patients irradiated on the brain raises
310 questions on the possible efficacy of cognitive rehabilitation. The study of Gehring et al.
311 studied the cognitive impact of cognitive rehabilitation programs in brain tumor patients. A
312 group of patients with brain tumor utilized from a computerized program of attention training
313 and learning of cognitive impairment rehabilitation techniques for 6 weeks. Another group of
314 control patients did not yet benefit from the cognitive Rehabilitation Program (waiting list).

315 Patients who had utilized the cognitive rehabilitation program presented significantly better
316 results in neuropsychological tests at 6 months compared with the control group [30]. Kesler
317 et al. found a beneficial effect of a computerized cognitive re-education program on executive
318 functions, verbal fluency and information-processing speed [31]. On account of brain
319 plasticity, cognitive rehabilitation should be interesting in this population. A clinical trial is
320 currently recruiting participants to assess the Impact of Cognitive Rehabilitation and Physical
321 Activity on Cognition in Patients with Metastatic Brain Tumors Undergoing RT
322 (NCT03096431).

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

329 **CONCLUSION**

330 This prospective pilot study suggests the interest of IHTTT in therapeutic management.
331 The IHT test would be a discriminatory test to assess cognitive function in evaluation of
332 patients with brain metastases irradiated by SRT. The IHTTT could become an assessment
333 tool to be considered as a new element in a therapeutic strategy.

334

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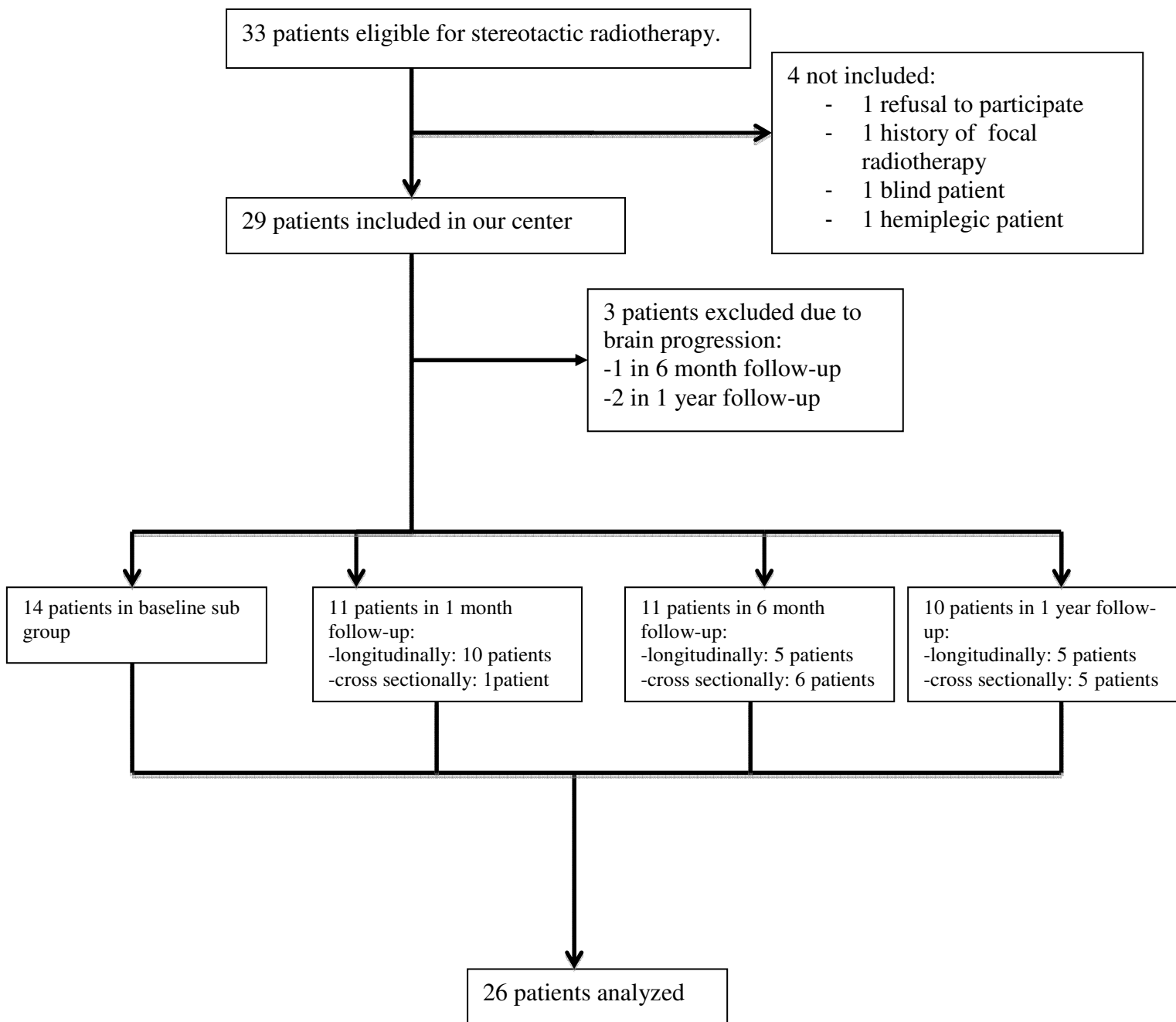


Figure I : Flow chart

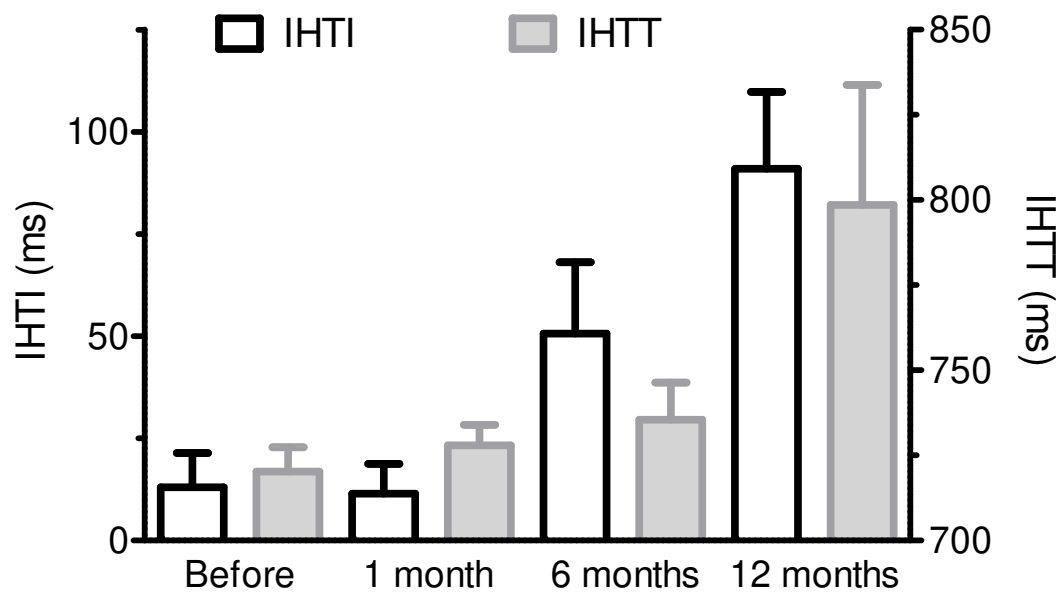


Figure 2. Evolution of IHTT and IHTI over time (mean and sd, milliseconds).

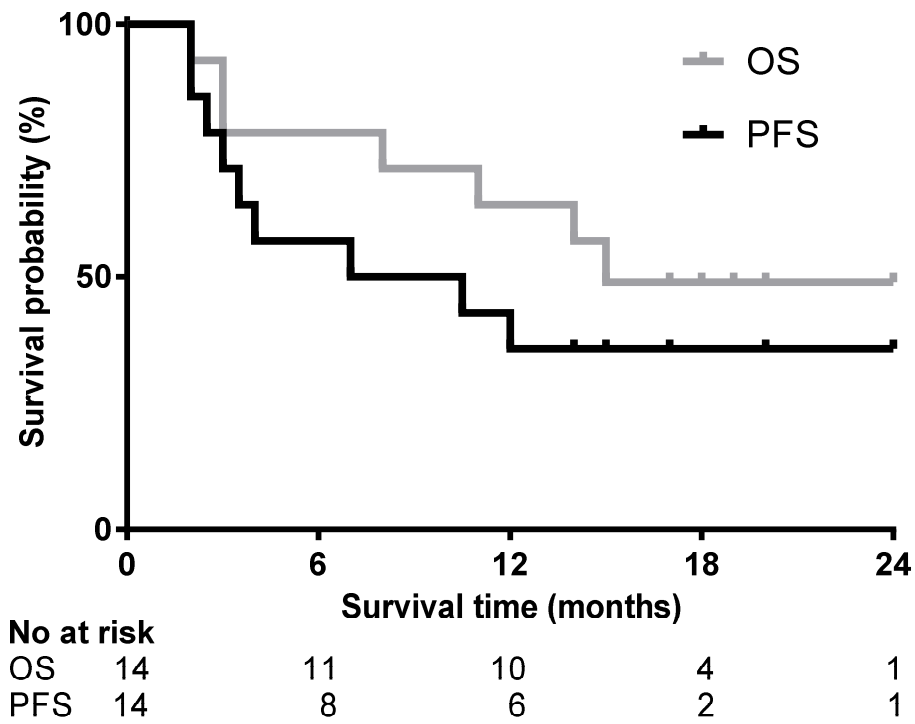


Figure 3. Overall survival (OS) and cerebral progression-free survival (PFS, months)

	Baseline	1 month	6 months	1 year
Patients (N)	14	11	11	10
<u>Age (y)</u>				
median (min-max)	58 (36-71)	60 (36-71)	61 (45-71)	62 (51-81)
mean \pm sd	56 \pm 10	58 \pm 11	60 \pm 7	65 \pm 10
<u>Sex (N, %)</u>				
Men	8 (57)	5 (45)	6 (55)	7 (70)
Women	6 (43)	6 (55)	5 (45)	3 (30)
<u>Brain metastases (N, %)</u>				
1-3	14 (100)	11 (100)	12 (100)	9 (90)
>3	0	0	0	1 (10)
<u>Metastases undergoing surgery (N, %)</u>				
RPA	5 (36)	4 (36)	2 (18)	4 (40)
1	4 (29)	3 (27)	6 (55)	4 (40)
2	10 (71)	8 (73)	5 (45)	6 (60)
3	0	0	0	0
<u>GPA (N, %)</u>				
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)
<u>Primary tumor (N, %)</u>				
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
<u>Metastasis diameter (N, %)</u>				
\geq 3 cm	5 (36)	4 (36)	1 (9)	3 (30)
<3 cm	9 (64)	7 (64)	10 (91)	7 (70)
<u>Tumor main axis (mm)</u>				
Mean \pm sd	25 \pm 16	24 \pm 17	17 \pm 7	24 \pm 21
median (min-max)	19 (6-60)	18 (6-60)	18 (6-30)	17 (7-61)
<u>Education (N, %)</u>				
< 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)
<u>Treatments (N, %)</u>				
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)

Table 1. Baseline characteristics of the patients.

	Before	1 month	6 months	1 year	<i>P</i>
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 2. Evolution with time of the cognitive tests and the quality of life scores.

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

r_s : Spearman nonparametric correlation coefficient

P: p-value of Spearman's test of correlation

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