Clinical and Translational Oncology

REGIONAL DEEP HYPERTHERMIA IN COMBINATION WITH WHOLE BRAIN RADIOTHERAPY (WBRT) IN POOR PROGNOSIS PATIENTS WITH BRAIN METASTASES.

--Manuscript Draft--

Manuscript Number:	CLAT-D-20-00145R1
Full Title:	REGIONAL DEEP HYPERTHERMIA IN COMBINATION WITH WHOLE BRAIN RADIOTHERAPY (WBRT) IN POOR PROGNOSIS PATIENTS WITH BRAIN METASTASES.
Article Type:	Brief Research Article
Keywords:	hyperthermia, radiotherapy, brain metastases
Corresponding Author:	Marta Lloret Saez-Bravo, Ph.D Hospital Universitario de Gran Canaria Dr Negrin Las Palmas de Gran Canaria, Las Palmas SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hospital Universitario de Gran Canaria Dr Negrin
Corresponding Author's Secondary Institution:	
First Author:	Marta Lloret Saez-Bravo, Ph.D
First Author Secondary Information:	
Order of Authors:	Marta Lloret Saez-Bravo, Ph.D
	Laura García-Cabrera
	Marta Zajac
	Pedro Carlos Lara, Ph.D.
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Purpose: The aim of this study is to assess for the first time, the role of regional deep hyperthermia in combination with radiotherapy and systemic therapy in patients with poor progonsis brain metastases (GPI≤2,5). Methods: Patients with confirmed cerebral metastases and classified as GPI score ≤2,5 were included in this prospective study. Pretreatment stratification was defined as patients with 0-1 GPI score (A group) and patients with 1.5-2.5 GPI score (B group). HT was applied twice a week, sixty minutes per session, during RT by regional capacitive device (HY-DEEP 600WM system) at 13,56 MHz radiofrequency. Results: Between June 2015 and June 2017, 15 patients and a total of 49 brain metastases were included in the protocol. All patients recieved all HT sessions as planned. RT and systemic therapy was also completed as prescribed. Tolerance to treatment was excellent and no toxicity was registered. Patients with HT effective treatment time longer than the median (W90time>88%) showed better acturial PFS at 6 and 12 months (100% & 66,7% respectively) compared with those with less treatment effective time HT treatment time (50% & 0% respectively) (p<0,031). Median OS was 6 months (range 1-36 months) . Stratification by GPI score, showed a median os of 3 months (CI 95% 2,49-3,51) in Group A and 8.0 months (CI 95% 5,15-10,41) in Group B (p=0,035). Conclusions: Regional hyperthermia is a feasible and safe technique to be used in combination with RT in brain metastases patients, improving PFS and survival in poor prognosis brain metastases patients.

TITLE PAGE:
REGIONAL DEEP HYPERTHERMIA IN COMBINATION WITH WHOLE BRAIN RADIOTHERAPY (WBRT) IN POOR PROGNOSIS PATIENTS WITH BRAIN METASTASES.

Lloret M.1,2,3, García-Cabrera L.1, Zajac M.1, Lara P.C3,4,5.

AUTHOR INFORMATION:
1 Department of Radiation Oncology, Dr. Negrin Hospital, Barranco de la Ballena s/n, 35010, Las Palmas de Gran Canaria, Spain. mllosae@gobiernodecanarias.org.
2 Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain. mllosae@gobiernodecanarias.org.
3 Instituto Canario de Investigación del Cáncer, Las Palmas de Gran Canaria, Spain.
4 Universidad Fernando Pessoa Canarias, Las Palmas, Spain.
5 Department of Oncology, Hospital Universitario San Roque, Las Palmas, Spain.

CORRESPONDING AUTHOR:
Marta Lloret Saez-Bravo
Dept Radiation Oncology, Dr Negrin Hospital,
Barranco de la Ballena s/n 35010
Las Palmas de Gran Canaria, Spain
Telf:0034928450284. Fax:0034928449127
mllosae@gobiernodecanarias.org
https://orcid.org/0000-0001-7273-4693

ABSTRACT
Purpose: The aim of this study is to assess for the first time, the role of regional deep hyperthermia in combination with radiotherapy and systemic therapy in patients with poor progonsis brain metastases (GPI≤2,5).
Methods: Patients with confirmed cerebral metastases and classified as GPI score ≤2,5 were included in this prospective study. Pretreatment stratification was defined as patients with 0-1 GPI score (A group) and patients with 1.5-2.5 GPI score (B group). HT was applied twice a week, sixty minutes per session, during RT by regional capacitive device (HY-DEEP 600WM system) at 13,56 MHz radiofrequency.
Results: Between June 2015 and June 2017, 15 patients and a total of 49 brain metastases were included in the protocol. All patients recieved all HT sessions as planned. RT and systemic therapy was also completedas prescribed. Tolerance to treatment was excellent and no toxicity was registered. Patients with HT effective treatment time longer than the median (W90time>88%) showed better acturial PFS at 6 and 12 months (100% & 66,7% respectively) compared with those with less treatment effective time HT treatment time (50% & 0% respectively) (p<0,031).
Median OS was 6 months (range 1-36 months). Stratification by GPI score, showed a median os of 3 months(CI 95% 2,49-3,51) in Group A and 8.0 months (CI 95% 5,15-10,41) in Group B (p=0,035).
Conclusions: Regional hyperthermia is a feasible and safe technique to be used in combination with RT in brain metastases patients, improving PFS and survival in poor prognosis brain metastases patients.

SHORT RUNNING TITLE: hyperthermia and radiotherapy in brain metastases

KEY WORDS: hyperthermia, radiotherapy, brain metastases

CONFLICTS OF INTEREST: No conflicts of interest

INTRODUCTION

Brain metastases (BM) are the most common type of intracranial neoplasms in adults and are one of the most common sites of metastasis in tumors [1]. Patients with BM have a very poor prognosis, but there is evidence that BM is a heterogeneus group with different survival outcomes. Prognostic indexes have been used in several malignancies in order to select patients and to aid the clinical and therapeutic decision making [2]. Prognostic Assesment (GPA) has become one of the most commonly used prognostic index in clinical practice [3] for BM. GPA incorporate four factors: age, Karnofsky performance status (KPS), presence of extracraneal disease (ECM) and number of metastases that impact in survival. Those patients with a GPA score ≤2,5 have a very poor prognosis and whole brain radiotherapy (WBRT) is usually prescribed as palliative treatment. In fact patients with GPA score of 0-1 had un expected survival of 2.6 months and those with a GPA score from 1.5-2.5 had an expected survival of 3.8 months [3].

Hyperthermia (HT) is used to treat tumors by increasing the temperature of the cells [4]. The temperatures required to treat tumors ranges from 39 to 43°C [5]. Biological effects of HT include trigger changes in perfusion and oxygenation as well as inhibition of DNA repair mechanisms. Moreover, there is evidence for immune stimulation and the induction of systemic immune responses [6]. Randomized phase III trials [7-9] and meta-analyses [10-12] demonstrated the increase in tumor response when HT is combined with oncological treatments.

There is no data available about the role of regional deep hyperthermia in patients with BM. In a recent publication [13] 63 BM patients were treated with intraoperative interstitial HT after complete surgical resection. Results of this study showed a significantly lower recurrence rate in the hyperthermia treatment group ($p<0.0003$) and suggest that intra-operative hyperthermia treatment could reduce local recurrence of tumor. Acute complications with this technique, such as focal seizure and wound infection, have been reported [13].

The aim of this study is to analyze the role of regional hyperthermia treatment combined with WBRT in poor prognosis (GPA score ≤2,5) brain metastases patients. The primary endpoint was to analyze results in terms of tumor progression and overall survival. Secondary endpoint was to assess the feasibility of the treatment and acute toxicity rate.

PATIENTS/METHODS

Study design and Participants

From June 1st 2015 to June 1st 2017, patients over 18 years old, suffering from brain metastases in different clinical situations, were classified using the GPA scale [3]. Patients with the worst prognosis (GPA score ≤2,5) were included in this study. Patients were stratified in two prognostic groups: very poor prognosis GPA<1.5 (group A) and poor/intermediate prognosis GPA 1.5-2.5 (group B).
Exclusion criteria were patients with metal protheses, pacemakers and pregnant women. Patients were followed prospectively under the Spanish RD 1566/1998 regulation for Radiotherapy Quality Assurance. The study was approved by the Ethic Committee and registered by number Eudract 2018-001089-40. Written inform consent for treatment was obtained in all patients. Standard of Care (SOC) systemic treatment and RT were used as per protocol and carefully assessed during the study. Follow-up was closed at february 2019 as all patients were death at that time.

Hyperthermia.

Heat was applied using an 13,56-MHz radiofrequency-capacitive regional HT (HY-DEEP 600WM system, Andromedic SRL, Velletri, Italy). HT was applied twice a week (every 72 hours) during all radiotherapy treatment schedule, as previously described [14]. Heating duration was prescribed to 60 min, and 150 watts were applied [15]. In all cases, electrodes were placed on opposite lateral sides of the patient's head, on supine position. Patients were carefully instructed to mention any unpleasant sensation suggestive of a hot spot [14].

Quality of HT was determined by the relation of energy and time of exposure during treatment. We previously defined [14] W90time and W90treat in order to get homogeneus parameters to analyze the quality of HT treatment. W90time is defined as the percentage of total treatment time at 90% of prescribed energy. W90treat was defined as the percentage of treatment sessions that reached 90% of prescribed energy.

Progression free survival (PFS) or overall survival (OS) were measured from the time of first treatment for each patient to the date of disease progression or death. Patients underwent weekly clinical assessments during the treatment to register toxicity. Toxicity was scored according to the integrated criteria (16) of the Common Toxicity Criteria Adverse Events (CTCAE 4.03) and Quality Management in Hyperthermia (QMHT). The highest toxicity grade reached for each patient during and after RT with regional HT, was used for the toxicity analysis. Delay in radiotherapy/systemic therapy due to HT was also recorded. Patients were followed by clinical assessment and brain MRI/Contrast enhanced CT-scan every 2-3 months unless symptomatic progression occurs. Actuarial analysis of PFS and OS was statistically compare by the Breslow-Wilcoxon test. All statistical analyses were performed using SPSS, Version 20.0 software (SPSS Inc., Chicago, IL).

RESULTS

Patients characteristics

Fifthteen patients (8 females and 7 males) and a total of 49 brain metastases were included in this prospective study. Mean age of our patients was 57 years (34-72). Main primary tumor location was lung (8 cases) and breast (4 cases), followed by one colorectal, cervix carcinoma and retroperitoneal sarcoma. All but 2 patients had more than one brain metastases. Median radiotherapy dose was 30 Gy (range 15-50 Gy). DBE 10 median dose was 39 Gy (22.4-75Gy). Six patients (37,5%) were classified as 0-1 GPA score (A group) and nine patients as 1.5-2.5 GPA score (B group) acording to GPA classification (Table 1).

Hyperthermia treatment feasibility and toxicity

All patients received all HT sessions planned(Mean 3,5 range 1-6*)*.The median W90time was 88% (50-100%) and 100% of sessions reached the 90% of prescribed energy (W90treat). Hyperthermia treatment was well tolerated in all patients, with no acute toxicity of any grade was present. All patients completed on time the scheduled WBRT and/or systemic treatment.

Analysis of Survival

Patientes were followed until death. Median Progression Free Survival (PFS) was 9 months (95%CI 7,66-10,33). Actuarial PFS was 68,6% and 17,1% at 6 and 12 months, respectively. PFS was longer in patients with longer hyperthermia effective treatment time (>88%W90time) compared to those with shorter effective treatment time (100%vs 50% at 6 months and 66,7% vs 0% at 12 months) (p=0.030) (Figure 1a). No relation with sex, primary tumour, DBE or GPA index were observed (Table 2).

Median OS was 6 months (1-36). Actuarial OS was 53,1% and 30,6% at 6 and 12 months, respectively. Only stratification by GPA score was predictive of survival (Table 2). A median OS of 3.0+/-0,26 months (95%CI 2,49-3.51) was observed in group A and compared to a median OS 8,0+/-1,45 months (95% CI 5,15-10,84) in group B. Actuarial 6 month Overal Survival was 16,7 % for group A vs 66,7% for group B (p= 0,035) (Figure 1b).

DISCUSSION AND CONCLUSIONS

Brain metastases (BM) results in significant morbidity and mortality among oncological patients. Palliative RT is the standard local treatment in the poor patient prognostic group (GPAscore ≤2,5), with poor results in terms of overall survival [3].

Combining hyperthermia (HT) and radiotherapy or chemotherapy, has shown to contribute to improve outcomes for patients in terms of overall survival and quality of life in several tumor locations [10-12]. To our knowledge this is the first study dealing with regional hyperthermia in patients brain metastases.

In our study 49 brain metastases from 15 patients that belongs to the most unfavorables GPA groups: 6 patients had an score index of 0-1 (A Group) and 9 patients had an score index of 1.5-2.5 (B Group) were included. All patients were treated with a combination of radiotherapy and regional HT.

The first conclussion of our study is that combined RT and regional HT is a well tolerated treatment in brain metastases patients. All treatments were administered as prescribed. No toxicity due to HT was registered. In contrast, Byun et al [13] in their study with intraoperative HT, described seizures and wound infection as complications of the combined treatment in a relevant number of cases. Deep hyperthermia seems to be easier and safe to administer than complicated intraoperative treatments.

Quality of HT treatment (W90time >88%) resulted in the strongest predicitve factor for survival. So patients who recieved >88% of the treatment time at 90% of the power prescribed (150W) had excelent PFS rates, acknowling the role of HT in sensitizing tumors to radiochemotherapy [4-7].

According to overall survival, median overall survival was 6 months in our serie, improving the poor results of standard treatment in these cases [3]. The association of hyperthermia to RT +/- systemic treatment achieved a 53,1% probability of remaining alive at 6 months and 30,6% at 12 months in our BM patients.

We also demonstrated for the first time that the patient´s overall survival was predicted by the GPA index in our series of combined RT+HT treatment. This results could support the use of this GPA index in this kind of patients.

When the observed patients´survival in our series is compared with the Sperduto results we could observe that for the poorest prognostic group (GPA <1.5) our 3 months observed survival is similary to the Sperduto [3] expected survival for these cases (2.7 months). Fortunately, in the intermediate/poor risk group (GPA 1.5-2.5) our data showed that observed survival in our series of patients is higher than expected (8.0 months vs 3.8 months).

Then, the third conclussion in our analysis is that we could have identified a subgroup of patients that even with brain metastases could benefit from the combined regional deep hyperthermia treatment.

These results are in line with the published evidence from Byum et al [13] in intraoperative HT after surgery. In these BM cases with good Karnosfky Status, few BM, controlled extracraneal disease and elegible to recieve surgical resection of the disease, intertitial HT combined with WBRT reduced the local recurrence rate ($p<0,0003$).

In conclusion, regional hyperthermia is a feasible and safe technique to be used in combination with RT in brain metastases patients, that seems to increase progression free survival. The GPA index is a reliable prognostic tool for predicting survival in patients under this combined treatment approach. According to the expected survival by the GPA index, patients in the poorest prognostic group (Group A) did´nt show any increase in survival by adding HT (2.6 vs 3 months). On the contrary, in patients in Group B (GPA score 1.5-2.5) the addition of hypertermia increased the overall survival from the expected 3.8 months to the observed 8.5 months. In selected patients with GPA score 1.5-2.5 there is a a significant improvement in overall survival.Major limitation of our study is the short number of patients included, and the very poor prognosis of most of them.

REFERENCES:

1. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012 Feb;14(1):48-54. doi: 10.1007/s11912-011-0203-y.

2. Nieder C, Mehta MP. Prognostic indices for brain metastases--usefulness and challenges. Radiat Oncol. 2009 Mar 4;4:10. doi: 10.1186/1748-717X-4-10.

3. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis- specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010 Jul 1;77(3):655-61. doi: 10.1016/j.ijrobp.2009.08.025.

4. Crezee H, van Leeuwen CM, Oei AL, et al. Thermoradiotherapy planning: Integration in routine clinical practice. Int J Hyperthermia 2015; 32(1): 41–49. doi: 10.3109/02656736.2015.1110757

5. Dewhirst MW, Vujaskovic Z, Jones E, et al. Re-setting the biologic rationale for thermal therapy. Int J Hyperthermia 2005; 21(8): 779–90. doi:10.1080/02656730500271668

6. Peeken JC, Vaupel P, Combs SE. Integrating hyperthermia into modern Radiation Oncology: what evidence is necessary? Front. Oncol. 2017; 7:132. doi: 10.3389/fonc.2017.00132

7. Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of super cial localized breast cancer: results from ve randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996; 35(4):731–44. doi:10.1016/0360-3016(96)00154-X

8. van der Zee J, González González D, van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000; 355(9210):1119–25. doi:10.1016/S0140-6736(00)02059-6

9. Kang M, Liu WQ, Qin YT, et al. Long-term eficacy of microwave hyperthermia combined with chemoradiotherapy in treatment of nasopharyngeal carcinoma with cervical lymph node metastases. Asian Pac J Cancer Prev 2013; 14(12):7395–400. doi:10.7314/APJCP.2013.14. 12.7395

10. De Haas-Kock DFM, Buijsen J, Pijls-Johannesma M, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database Syst Rev 2009; 3:CD006269. doi:10.1002/14651858.CD006269.

11. Datta NR, Puric E, Klingbiel D, et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys 2016; 94(5): 1073–1087. doi:10.1016/j.ijrobp.2015.12.361

12. Lutgens LCHW, Koper PCM, Jobsen JJ, et al. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: results of the randomized RADCHOC trial. Radiother Oncol 2016; 120(3): 378–82. doi:10.1016/j.radonc.2016.02.010

13. Byun YH, Gwak HS, Kwon JI, et al (2018): Local recurrence of brain metastasis reduced by intra-operative hyperthermia treatment. Int J Hyperthermia. 2019 Jan 1;35(1):168-175. DOI: 10.1080/02656736.2018.148800

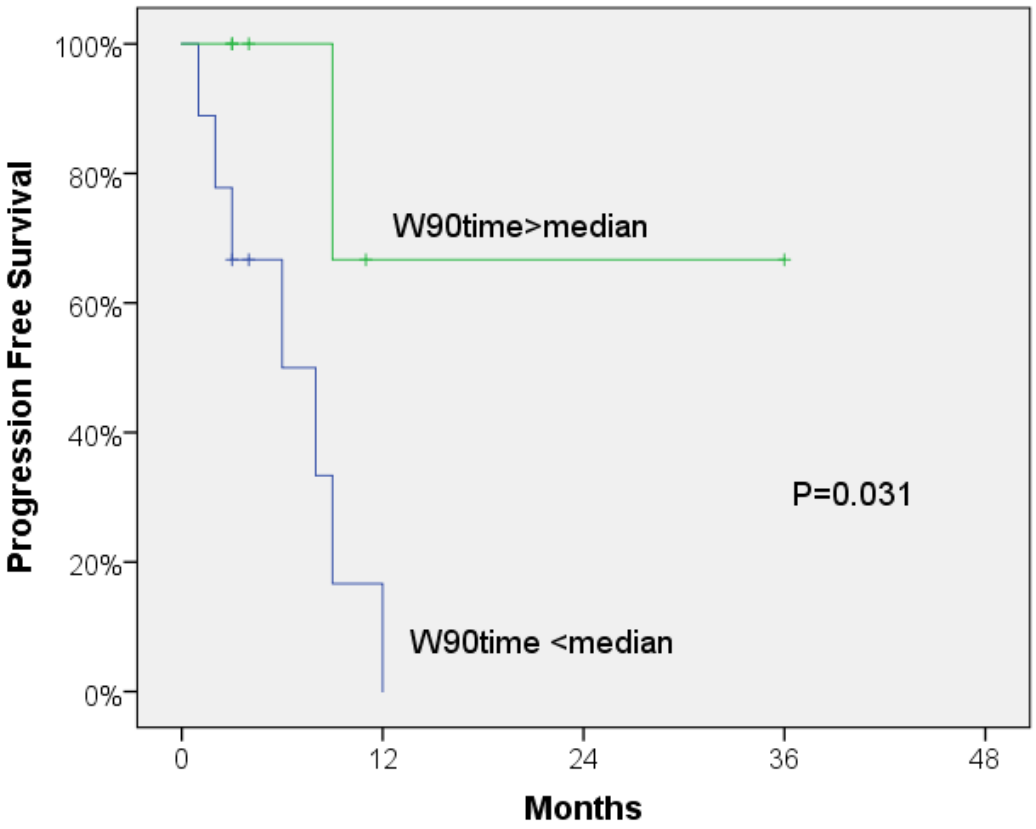
14. Lloret, M., García-Cabrera, L., Hernandez, A. et al. Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors: first Spanish experience. Clin Transl Oncol (2019). https://doi.org/10.1007/s12094-019-02097-9

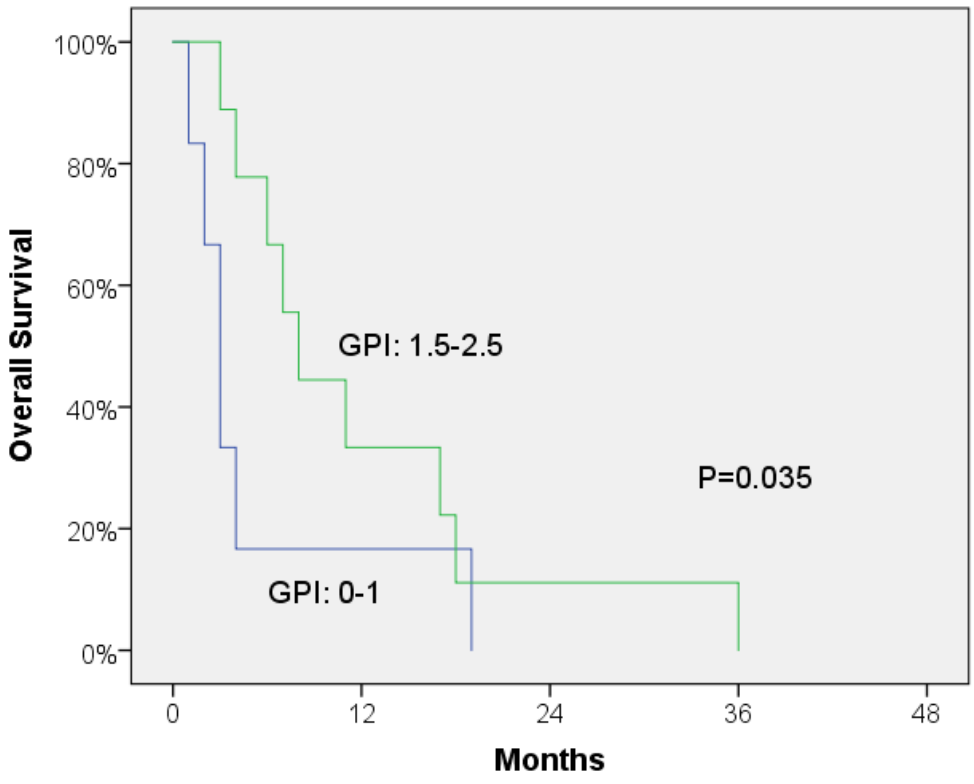
15. Sahinbas H, Rosch M, Demiray M. Temperature measurements in a capacitive system of deep loco-regional hyperthermia. Electromagnetic Biology and Medicine 2017; 36:3, 248-258. doi: 10.1080/15368378.2017.1307221

16. Bruggmoser G, Bauchowitz S, Canters R, et al. Quality assurance for clinical studies in regional deep hyperthermia. Strahlenther Onkol 2011; 187(10): 605–610. doi:10.1007/s00066-011-1145-x

FIGURES

Figure 1. a) Progression Free Survival by Hyperthermia effective treatment time b) Overall survival by GPI score.





TABLES

Table 1. Score and number of patients by different factors in our serie.

GPA Factor	SCORE		
	0	0.5	1
Age Patients	>60y (8)	50-59y (3)	<50y (4)
KPS Patients	<70% (3)	70-80% (7)	90-100% (5)
Brain Metastases Number Patients	>3 (6)	2-3 (7)	1 (2)
Extracraneal disease Patients	Yes (12)		No (3)

Table 2. Actuarial PFS and survival acording to risk factors

	PFS 6 months	Univariate P value	OS 6 months	Univariate P value
Sex				
Male (8)	71.4%		28.8%	
Female (7)	70.0%	.442	62.5%	.107
Primary Tumor				
Lung (8)	87.5%		37.5%	
Breast (4)	75.0%	.900	100%	.100
GPI				
0-1 (6)	66.7%		16.7%	
1.5-2.5 (9)	74.1%	.224	66.7%	**.035**
DBE				
≤39Gy (8)	45.0%		62.5%	
>39Gy (7)	85.7%	.257	28.6%	.415
W90time				
≤88% (8)	50.0%		50%	
>88% (7)	100%	**.031**	42.9%	.773