**Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia**

**ED Hager, H Sahinbas, DH Groenemeyer, F Migeod; Biomed-Hospital & University Witten-Herdecke, Germany**

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### Background

Treatment of malignant gliomas is in spite of many new approaches still disappointing. Median survival time (MST) of pts. with glioblastoma multiforme (GM) after diagnosis is 6 to 12 months. **Surgery** is treatment of first choice, but in most cases healing is not possible. The aim of surgery are tumor resection or decompression of the brain. **Radiotherapy** will double MST after surgery but high grade gliomas are not very radiosensitive. Survival **Concurrent radiation with temozolomide** could increase median survival time of pts with GM from 12.1 to 14.6 months.

### Rationale for Hyperthermia

- Lower thermal doses (mild to moderate T):
  - protein denaturation, esp. nuclear matrix
  - increased blood perfusion → tumor oxygenation ↑
  - reduction of intratumoral pressure
  - reduction in DNA repair capacity
  - anti-cancer immunoresponse, stimulation of innate and adaptive immune response
  - increase in uptake of drugs
- Higher thermal doses:
- cytotoxic, increases tumor necrosis & apoptosis
- vascular destruction & anti-angiogenic effects
- synergistic response to RTx/CTx/txx/geneTx
- Non-thermal effects:
- electromagnetic coupling, interstitial heating

### Methods & Technical Devices

**a) Technical Devices**

- **Radiative**
- **Capacitive**
- **Inductive**

**Technical Decision Making:**

- **Radiative**
- **Capacitive**
- **Inductive**
  - Indications for hot spots (indicated, selective heating and non-thermal effects indicated with nanoparticles or liposomes containing Fe)

**b) Electromagnetic (15.36 MHz) vs heat**

### Case Report #: Anaplastic Astrocytoma (WHO® III)

**Patient Characteristics**

- Accrual time from 02/2000 to 04/2007
- 53 pts. with anaplastic astrocytoma (WHO® III)
- 126 pts. with glioblastoma multiforme (WHO® IV)
- Median age (range):
  - AA: 40 yrs
  - GM: 49 yrs
- Karnofsky Performance Score (range):
  - AA: #
  - GM: #

### Primary Therapies:

- **LRF-DHT**
- **Radiation**
- **Chemotherapy**

### Results:

Complete data where collected from all pts. and considered for evaluation if at least 1 cycle of LRF-DHT could be performed. The median follow-up time was for AA: # and GM: # months.
Median age: 43.9 yrs.

- The median overall survival times (MST) with confidential intervals are listed in table 1 and the survival probabilities in table 2. Complete and partial remissions could be achieved in both groups by LRF-DHT alone.

### Table 1: MST of patients with WHO® III & IV gliomas (Kaplan-Meier Estimation)

<table>
<thead>
<tr>
<th>Condition</th>
<th>MST from</th>
<th>AA: N = 53 pts</th>
<th>GM: N = 126 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>38.24±3.5 [31.34;55.0]</td>
<td>20.3±4.7 [17.0;23.6]</td>
<td></td>
</tr>
<tr>
<td>1. LRF-DHT</td>
<td>10.6±2.0 [6.7;14.4]</td>
<td>7.6±1.9 [5.9;9.3]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>N (%)</th>
<th>AA: 40 (40%)</th>
<th>GM: 40 (40%)</th>
</tr>
</thead>
</table>

### Table 2: Survival probability (Kaplan-Meier Estimation)

<table>
<thead>
<tr>
<th>Time [months]</th>
<th>AA WHO® III</th>
<th>GM WHO® IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yrs</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2 yrs</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>3 yrs</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>4 yrs</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>5 yrs</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

### Adverse effects:

- **A) Short-term (2h) anemia after treatment (8-10%)**
- **B) Local redness (rubor) of the skin (8%)**
- **C) Edema of (fresh) scars (<1%)**
- **D) Complications:**
  - Subcutaneous fibrosis of fat tissue (1%)
  - Burning sensations stage I-II (2%)**
  - Headache, fatigue & nausea (1-2 days) (12%)**

### Summary & Conclusions:

- **DHT with capacitive coupled electrodes with low radiofrequency (15.36 MHz) is feasible without any severe side effects, and even pts. at advanced stages of disease could be treated.**
- Complete and long duration partial remissions or stable disease is possible.
- A significant prolongation of survival after resection and progression after 1st line therapy could be demonstrated.
- Further randomized trials are warranted.

**[Other Information]**


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