Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)

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Introduction
Aggressive malignant tumors are known to be usually hypoxic. It’s well known that hypoxia decreases tumors’ response to radiotherapy (radiosensitivity). At least 2 or 3 times more radiation dose is needed to kill hypoxic cells compared with well oxygenated cells.
Several studies have shown that modulated electro hyperthermia (mEHT) is able to increase tumor oxygenation, and thus alleviate the hypoxia that would lead to greater radioresistance, establishing itself as an optical moment to apply radiotherapy, about 30 minutes after the treatment of mEHT.
There are also several studies showing the efficacy of mEHT in killing cancer cells when used alone without any other cancer treatments.
These are some of the reasons why the combination of these treatments (mEHT + Radiochemotherapy) could result on an improvement in tumor control and survival for cancer patients. Despite several studies about mEHT treatment in cancer patients alone or combined with standard radio-chemotherapy have been published with wonderful results, we still do not have enough phase III trials to clarify the role of mEHT on cancer treatment.

Purpose
To perform three different phase III clinical studies to test whether the combination of radiochemotherapy treatment with mEHT in the 30 minutes prior to the radiotherapy session, or the treatment in monotherapy with mEHT in those cases not susceptible to another oncological treatment, will improve local control (primary objective) and/or survival (secondary objective) in patients with high-grade brain tumors, pancreatic cancer or rectal cancer, without increasing side effects from the standard treatments.

Material and methods
Patients diagnosed with high grade glioma, pancreatic cancer, or rectal cancer will be included in three different phase III clinical studies. These studies will include newly diagnosed cancer patients or patients with recurrent malignant tumors after treatment with standard therapies. The study for patients diagnosed with high grade brain glioma (stages III and IV) will include patients who will receive treatment in an adjuvant setting after surgery combining mEHT with standard chemo-radiotherapy or with mEHT as the only treatment in those cases not candidates to surgery, chemo and/or radiotherapy. The clinical study about pancreatic cancer, will include patients with locally advanced cancer and again, mEHT treatment will be combined with the standard chemo-radiotherapy treatment in a neoadjuvant, radical, palliative or adjuvant setting, or will be the unique treatment in those cases not amenable to be treated with standard therapies. The third study, is for patients diagnosed with rectal cancer who meet the criteria to receive standard treatment with neoadjuvant chemo and radiotherapy, in whom mEHT will be combined with these neoadjuvant treatments. In all the studies, when mEHT is combined with radiotherapy, it will be always delivered around 30
minutes before each radiotherapy session. Patients with history of other cancer in the past 10 years will be excluded.

**Results**
Three different phase III clinical studies have been already designed to be performed at the radiation oncology department of Valdecilla University Hospital in Santander, Spain. We have already received the approval of the University Hospital Marqués de Valdecilla and the “Idival” research institute, which will be also a collaborator, to begin with the studies, and we also have the necessary insurances to run them. We have also appointed a coordinator to control and check the proper development of these studies.

**Conclusion**
Modulated electro hyperthermia combined with standard radio and chemotherapy or as a unique treatment in cancer patients not candidate to standard treatment, looks very promising to improve local control and survival in cancer patients. These clinical studies will give us very valuable information about the role of mEHT in cancer treatment, and its contribution as a radiotherapy and chemotherapy sensitizer.
Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)

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Budapest, September 28th 2018

WHAT I WILL TALK ABOUT?

• Introduction
• Cancer Statistics
• Radiotherapy
• Some of our projects to solve/improve our cancer treatment results
  • Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)
• Take home messages - conclusions
INTRODUCTION...

University Hospital Marqués de Valdecilla
Santander, Spain

**Radiotherapy department:**
- Team: 62 people.
- 11 Radiation oncologists.
- External beam radiotherapy:
  - 3 linear accelerators:
    - Radiosurgery
    - Stereotactic RT (intra and extracranial)
    - Image guided RT
    - Intensity modulated RT
- 2 operating rooms for Brachytherapy
  - HDR and LDR
  - Intraoperative radiotherapy

**Main aim is:**
- CURE CANCER
- Without toxicities

CANCER STATISTICS

>18 million NEW cancer cases in 2018 (Globocan 2018)

> 45% will die from cancer:

- Depending on:
  - Country
  - Race
  - Sex
  - Type of cancer
  - Stage
  - Treatment

Estimated number of deaths in 2018, worldwide, all cancers, both sexes, all ages

Total: 9,555,027
CANCER STATISTICS

- ESTIMATED NUMBER OF NEW CANCER CASES IN 2018 (ALL AGES, BOTH SEXES) 18,078,957
- ESTIMATED NUMBER OF DEATHS BY CANCER IN 2018 (ALL AGES, BOTH SEXES) 9,555,027

> 45% cancer patients will die from cancer. NOT ENOUGH!!!

HELP

NEW TREATMENTS

RADIOTHERAPY

- According to the American Society of Radiation Oncology (ASTRO), **more than 60% of cancer patients will receive radiation therapy** - either alone or in combination with other treatment approaches, such as surgery and chemotherapy.

- Only improving radiation therapy results → we will improve results in more than 60% of cancer patients.
RADIOTherapy

- Very powerful tool → able to kill “anything”
  - Power to kill depends on type of energy...
  - but mainly dose

“We cannot kill all cancer cells with radiation in some tumors, because we cannot give enough dose”

Tumors can be:

- **Radiosensitive** → dye “easily” with radiation. (With acceptable radiation doses for healthy tissues).
- **Radioresistant** → dye with “higher” radiation doses [Not tolerable for healthy tissues].

TUMOR RADIORESISTANCE

- Clinically, a tumor is considered radioreistant when irradiation is unable to reduce its volume or when a recurrence occurs after a possible regression. Four general characteristics are currently used to predict tumor radiocurability:
  
  - **The number of clonogenic cells**: the probability of local control depends on the number of clonogenic cells present in the tumor at the beginning of treatment. When more clonogenic cells are present, the tumor presents a higher risk of radioresistance.
  
  - **The kinetics of tumor growth**: and tumor cell proliferation: after radiotherapy, a small number of surviving tumor cells can gradually and slowly proliferate and reestablish the tumor (fractionation). The greater the number of proliferating cells, the higher the likelihood that the tumor will be radiosensitive.
  
  - **The number of hypoxic cells**: cells that are hypoxic or anoxic at the time of irradiation suffer less damage from a given radiation dose than do oxygenated cell → poorly vascualized areas within tumors is an important component of tumor radioresistance. A greater number of hypoxic cells within a tumor makes it more radioresistant.
  
  - **The intrinsic radiosensitivity**: intrinsic radiosensitivity is the cell’s own response to radiation, that is, its implementation of radioresistant molecular mechanisms. This factor depends primarily on the integrity of the cell’s detection and repair of DNA damage, but it is also affected by intercellular communication and the cell’s response to growth factors.
TUMOR “RADIOCURABILITY”:

- **The number of clonogenic cells:**
  - More cells, more radioresistant
  - We cannot change this (“we have what we have” at diagnosis).

- **The kinetics of tumor growth**
  - More growth, more radiosensitive
  - We might change this

- **The number of hypoxic cells**
  - More hypoxic, more radioresistant
  - We **may** change this up to date

- **The intrinsic radiosensitivity**
  - We might change this
TUMOR “RADIOCURABILITY”

- **The number of hypoxic cells**
  - More hypoxic $\rightarrow$ more radioresistant and more “chemo-resistant”
  - We may change this up to date

- Great amount of studies with different drugs to decrease hipoxia $\rightarrow$ radiosensitizers
  - Discouraged by the predominantly negative results of the clinical trials (side effects, low efficacy...)

HEAT $\rightarrow$ INCREASE BLOOD FLOW $\rightarrow$ INCREASE OXYGEN

HYPERTHERMIA

ARE TUMORS REALLY MORE HYPOXIC?

Comparison of the oxygenation in organs and respective tumors

<table>
<thead>
<tr>
<th>Tissue/organ</th>
<th>Hypoxia (median % $O_2$)</th>
<th>Cancer</th>
<th>Hypoxia (median % $O_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>4.6</td>
<td>Brain tumor</td>
<td>1.7</td>
</tr>
<tr>
<td>Breast</td>
<td>8.5</td>
<td>Breast cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>Cervix</td>
<td>5.5</td>
<td>Cervical cancer</td>
<td>1.2</td>
</tr>
<tr>
<td>Kidney cortex</td>
<td>9.5</td>
<td>Renal cancer</td>
<td>1.3</td>
</tr>
<tr>
<td>Liver</td>
<td>4.0–7.3</td>
<td>Liver cancer</td>
<td>0.8</td>
</tr>
<tr>
<td>Lung</td>
<td>5.6</td>
<td>Non-small-cell lung cancer</td>
<td>2.2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7.5</td>
<td>Pancreatic tumor</td>
<td>0.3</td>
</tr>
<tr>
<td>Rectal mucosa</td>
<td>3.9</td>
<td>Rectal carcinoma</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Yes, they are!!!

TUMOR HYPOXIA

- Evidence has shown that 50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue areas that are distributed heterogeneously within the tumor mass.
- Hypoxia arises in tumors through the uncontrolled oncogene-driven proliferation of cancer cells in the absence of an efficient vascular bed.
- Data do not suggest a topological distribution of the pO2 values within a tumor.
- Tumor-to-tumor variability in oxygenation is greater than intratumor variability.
- Local recurrences have a higher hypoxic fraction than the respective primary tumors, although there is no clear cut difference between primary and metastatic malignancies.
TUMOR HYPOXIA

• Results from a mismatch between the oxygen supply by poorly efficient blood vessels and oxygen consumption by metabolically overactive tumor cells.

• Three main forms of hypoxia:
  • **Diffusion-limited hypoxia**: A gradient of oxygen deprivation from the nearest perfused blood vessels toward tumor cells at increasing distances from this vessel. It originates from high-rate of oxygen extraction though layers of cells within a loosened vascular network.

![Diagram of Tumor Hypoxia](image)

TUMOR HYPOXIA

• Three main forms of hypoxia:
  • **Diffusion-limited hypoxia**.
  • **Perfusion-limited hypoxia**: Oxygen deprivation along the vascular tree from the tumor margin toward the tumor core.
    • Poor oxygen delivery has many causes in tumors, including high-rate of oxygen extraction at the tumor margin, decreased red blood cell deformability, and stacking, increased blood viscosity due to water extraction, vascular disorganization, and angiogenesis.
    • Arrows represent the blood flow.
TUMOR HYPOXIA

• Three main forms of hipoxia:
  • **Diffusion-limited hipoxia.**
  • **Perfusion-limited hipoxia.**
  • **Anemic hypoxia**: reduced O₂ transport capacity of the blood subsequent to tumor-associated or therapy-induced anemia.
    • Experimental studies have shown that the O₂ supply to tumors is greatly reduced and hypoxia is intensified at hemoglobin levels below 10–12 g/dl, especially when low O₂ transport capacity coincides with a low perfusion rate.

WHY HYPOXIA INCREASES RADIORESISTANCE?

• The lack of oxygen leads to decreased production of reactive oxygen species and consequently to reduced DNA damage after conventional radiotherapy with high energy photons.
• There is a relationship between decreased oxygen tension and gradual decline of radiation cell killing changing with different radiation qualities.
HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

- In biological tissues, irradiation primarily induces water ionization and destabilization, leading to the formation of reactive radical species.

- These species then react with neighboring molecules to yield reactive oxygen species (ROS), among which the hydroxyl radical is believed to be the most cytotoxic.

HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

- When generated in the proximity of DNA, hydroxyl radicals and, to a lesser extent, other less energetic species attack DNA. The resulting formation of a DNA radical is readily reversible.

- However, in the presence of oxygen, DNA damage can be stabilized through oxidation of DNA radicals, eventually leading to the formation of DNA peroxides.

- In oncology, oxygen-dependent DNA damage fixation is known as the “oxygen enhancing effect” of radiotherapy.
HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

- And the hypoxia does not only determine “radiosensitivity” but also...
  - RT fractionation:
    - For several reasons, RT is normally administered as a fractionated regimen.
    - One of the reasons is because there is improved targeting of previously hypoxic cells, as they reoxygenate between fractions.

![Diagram showing hypoxic cells and reoxygenation.](image)

The proportion of hypoxic cells is lower in radiated vs not radiated tumors.

THE ROLE OF “mEHT” IN CANCER TREATMENT

- Several studies have shown that modulated electro hyperthermia (mEHT) is able to increase tumor oxygenation.
  - → Decrease the hypoxia
  - → Increase radiosensitivity

- An optimal moment to apply radiotherapy, about 30 minutes after the treatment with mEHT.
“mEHT AS A RADIO-CHEMOSENSITIZER”

• eMHT improves blood flow → decreases hypoxia


Lee BS, Hwang EK, Lee JH, Hwang YH, Lee JH, Choi DH.

Author Information

Abstract

INTRODUCTION: Mild hyperthermia has been known to enhance the response of tumours to radiotherapy or chemotherapy by increasing tumour blood flow, thereby increasing tumour oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

METHODS: The pelvis area of 20 patients with cervical carcinoma was heated with mEHT. The per-tumour temperature was measured using an internal organ temperature probe. The tumour blood flow was measured using 3D colour Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (SD ratio) and the resistance index (RI) within blood vessels.

RESULTS: The mean per-tumour temperature was 36.7 ± 0.2 °C before heating and increased to 36.5 ± 0.8 °C at the end of heating for 80 min. The marked declines in RI and SD values strongly demonstrated that heating significantly increased tumour blood perfusion.

CONCLUSIONS: Regional heating of the pelvis area with mEHT significantly increased the per-tumour temperature and improved the blood flow in cervical cancer. This is the first demonstration that the blood flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.

“mEHT” IN CANCER TREATMENT

• There are also several studies showing the efficacy of mEHT in killing cancer cells when used alone without any other cancer treatments.

• mEHT kills cancer cells by apoptosis
  • No necrosis
  • Less toxic

Selective

Representative histology images of untreated control, 1% heated and 2% treated cells. (A) Representative histology images of untreated control, 1% heated and 2% treated cells. (B) Immunostaining of the 1% heated and 2% treated cells. (C) Immunostaining of the 1% heated and 2% treated cells. (D) Immunostaining of the 1% heated and 2% treated cells. (E) Immunostaining of the 1% heated and 2% treated cells.

“mEHT” IS SELECTIVE

“mEHT” AS A CANCER CELL “KILLER”

Electro-hyperthermia inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis.

Abstract

PURPOSE: Modulated electro-hyperthermia (mEHT), also known as oncotherapy, inhibits tumorigenicity by inducing apoptosis. In the present study, we investigated whether mEHT induces apoptosis in glioma cells.

MATERIALS AND METHODS: U87-MG and A172 human glioma cells were exposed to different concentrations of mEHT and assessed for apoptosis using flow cytometry and Western blotting. mEHT treatment was performed using a hyperthermic applicator with a power output of 1 W/cm² for 2 hours.

RESULTS: mEHT induced apoptosis in glioma cells by selectively targeting tumor cells. The extent of apoptosis was dose-dependent, with the highest apoptosis observed at 10 W/cm². mEHT treatment also upregulated the expression of pro-apoptotic genes, such as Bax and Bad, and downregulated the expression of anti-apoptotic genes, such as Bcl-2.

CONCLUSIONS: These findings suggest that mEHT suppresses glioma cell proliferation and induces apoptosis through the induction of E2F1-mediated apoptosis and might be an effective treatment for eradicating brain tumors.
THE ROLE OF “mEHT” IN CANCER TREATMENT

- **Modulated electro hyperthermia is able to increase tumor oxygenation.**
  - Increase radiosensitivity
  - Increase chemosensitivity
- **Modulated electro hyperthermia is able to kill by apoptosis malignant cells**

- These are some of the reasons why the combination of mEHT + Radio-chemotherapy, could result on an improvement in tumor control and survival for cancer patients.

ADDING EFFORTS...

![Diagram showing different treatment options including surgery, chemotherapy, and radiation, with eMHT and improved outcomes]

- **TUMORS RT-CHEMORESISTANT**
  - IMPROVE TUMOR CONTROL
  - IMPROVE SURVIVAL
  - NOT INCREASE TOXICITIES
WE HAVE MANY STUDIES ABOUT “mEHT”...

Glioma efficacy study (Phase II), (n=53+126) & (n=9+27)

Clinical study for advanced pancreas oncothermia...

BUT STILL, NOT ENOUGH...

SO, LET’S DO “ENOUGH”...
University Hospital Marqués de Valdecilla

- One of the “top” public hospitals of Spain.
- Very soon the first public hospital in Spain to have an meHT device.

Virtual Hospital Valdecilla

- A pioneer center in Europe in the use of clinical simulation for the training of health professionals and the improvement of patient safety.
- Works in collaboration with the Center for Medical Simulation (Boston)

IDIVAL Research Institute

In March 2015 IDIVAL was awarded by the Spanish Institute of Health Carlos III as one of the reference Institutes for Health Research in Spain

WHICH TUMORS \( \rightarrow \) THE DIFFICULT!!!

Radiosensitivity

- 17 tumor types were placed in 5 categories.
- Categories A to E with decreasing sensitivity.
- A: Lymphoma, Myeloma, Neuroblastoma.
- B: Medulloblastoma, CLC
- C: Glioblastoma, RCC
- D: Pancreas, Colo-Rectal, Squamous Lung
- E: Melanoma, Osteosarcoma, Glioblastoma, RCC

The radiosensitivity of human tumours and the initial slope of the cell survival...
GLIOBLASTOMA AND GRADE III ASTROCYTOMA

- Glioblastoma multiforme (GBM), a grade IV astrocytoma, is the most common and deadly type of primary malignant brain tumor.

CENTRAL NERVOUS SYSTEM CANCER

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2018</th>
<th>Estimated Deaths 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>268,120</td>
<td>40,920</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>224,060</td>
<td>134,900</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>164,880</td>
<td>28,430</td>
</tr>
<tr>
<td>4. Colorectal Cancer</td>
<td>140,200</td>
<td>58,030</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>91,279</td>
<td>9,335</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>81,199</td>
<td>17,240</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>74,889</td>
<td>13,050</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>65,943</td>
<td>14,970</td>
</tr>
<tr>
<td>9. Uterine Cancer</td>
<td>63,230</td>
<td>11,250</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>60,508</td>
<td>24,370</td>
</tr>
<tr>
<td>11. Brain and Other Nervous System Cancer</td>
<td>22,080</td>
<td>10,850</td>
</tr>
</tbody>
</table>

Brain and other nervous system cancer represents 1.4% of all new cancer cases in the U.S.

Estimated New Cases in 2018: 2,200,660
Estimated Deaths in 2018: 1,603,000

Percent Surviving 5 Years: 33.2% (2006-2014)
CENTRAL NERVOUS SYSTEM CANCER

- The current treatment for GBM involves tumor resection surgery based on MRI image analysis, followed by radiotherapy and treatment with temozolomide.
- Radiotherapy alone can significantly increase median survival, although the most common radiological response is to stabilize the disease but ultimately tumor progression follows.
- Despite treatment, patient’s median survival rate ranges from 15 to 17 months.

GLIOBLASTOMA SURVIVAL

Figure 2: Survival Curves by Histologic Subtype for Individuals Who Received Resection by Race or Ethnicity, Adjusted by Age and Extent of Resection (Subtotal vs Gross Total), 2000-2014
HIGH GRADE GLIOMA TUMORS

- High grade glioma tumors (grade III and IV) are radioresistant.
- Several reasons for radioresistance:
  - **The number of clonogenic cells**:
    - More cells, more radioresistant
  - **The kinetics of tumor growth**:
    - More growth, more radiosensitive
  - **The number of hypoxic cells**:
    - More hypoxic, more radioresistant
    - The clinical-pathological effects of hypoxia in GBM can be observed by magnetic resonance imaging (MRI) where significant oxygen diffusion restriction is detected, consistent with absent or defective blood flow
  - **The intrinsic radiosensitivity**

RECTAL CANCER

- Colorectal cancer: 4th most common cancer diagnosed in both men and women in the world (3rd in USA).
- Rectal cancer: 9th
COLORECTAL CANCER SURVIVAL

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2018</th>
<th>Estimated Deaths 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast (Female)</td>
<td>286,110</td>
<td>46,000</td>
</tr>
<tr>
<td>2. Lung and Bronchial</td>
<td>294,000</td>
<td>154,050</td>
</tr>
<tr>
<td>3. Prostate</td>
<td>186,990</td>
<td>29,682</td>
</tr>
<tr>
<td>4. Colorectal Cancer</td>
<td>140,350</td>
<td>39,070</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>81,270</td>
<td>9,010</td>
</tr>
<tr>
<td>6. Kidney Cancer</td>
<td>81,590</td>
<td>11,240</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>74,600</td>
<td>13,230</td>
</tr>
<tr>
<td>8. Melanoma and Renal Pelvis Cancer</td>
<td>65,340</td>
<td>14,970</td>
</tr>
<tr>
<td>9. Uterine Cancer</td>
<td>60,250</td>
<td>11,380</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>60,300</td>
<td>31,370</td>
</tr>
</tbody>
</table>

SEER 18 2011-2015, All Races, Both Sexes

RECTAL BUT NOT COLON CANCER

- Rectal cancer and not colon cancer → Why?
  - Because we don’t treat colon cancer with radiotherapy.
IMPROVING TREATMENT...

3 STUDIES:
- HIGH GRADE GLIOMA
- RECTAL CANCER
- PANCREATIC CANCER

HIGH INCIDENCE / MORTALITY / YOUNG PEOPLE

Surgery
Treatment options
Radiation
Chemotherapy
eMHT

COMMON POINTS FOR THE 3 STUDIES

5. STUDY DESIGN
This is a prospective, randomized study designed to evaluate the possible benefit in terms of better control of the disease, of adding a treatment with modulated electrohyperthermia to standard surgery, radio and chemotherapy treatments or as a single treatment in those cases that meet the inclusion criteria of the study and in which it is not possible to apply any other treatment.

It is hypothesized that treatment with modulated electrohyperthermia, will produce different beneficial effects that will impact on better oncological control such as:
- Radiosensitivity: mEHT will increase oxygenation and therefore will decrease hypoxia, improving this way radiosensitivity in those patients who will receive radiotherapy treatment concomitantly with mEHT.
- Chemosensitivity: mEHT will increase oxygenation and improve blood flow to improve the "drugs" distribution in the tumor area.
- Improve cancer cell killing: mEHT will promote cancer cell destruction through apoptosis by a mechanism of selection and modulation.

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COMMON POINTS FOR THE 3 STUDIES

**PRETREATMENT DIAGNOSIS:**
- Complete clinical history including toxic habits, oncologic and laboral history.
- Physical examination.
- Complete anatomopathological report.
- Diagnostic imaging tests as indicated in the gold standard guidelines for cancer treatment.
- Assessment of QoL.

**FOLLOW-UP DURING TREATMENT:**
- Weekly visit with the radiation oncologist to evaluate toxicities from the treatment.

**FOLLOW-UP AFTER TREATMENT:**

- **3 weeks after treatment:**
  - Physical exam (toxicities). No imaging test unless recommended for any special condition.

- **1-3 months after treatment (depending on the tumor):**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.

- **6 months after treatment:**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.

- **From 6th month ➔ visits every 3 months:**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.
**INCLUSION CRITERIA**

<table>
<thead>
<tr>
<th>HIGH GRADE GIOMA</th>
<th>RECTAL CANCER</th>
<th>PANCREATIC CANCER</th>
</tr>
</thead>
</table>
| Confirmed by pathology **High Grade Glioma (III and IV)**  
  - Newly diagnosed patients  
  - Patients with relapse/progression. | Confirmed by pathology, imaging, and physical exam, **Stage II** (T3-4, node-negative disease with tumor penetration through the muscle wall) or **stage III** (node-positive disease without distant metastasis) **rectal cancer**.  
  - Patients who will receive **neoadjuvant standard treatment with chemo-RT**. | Confirmed by pathology, imaging, and physical exam **pancreatic adenocarcinoma**.  
  - Patients candidates to neoadjuvant chemoradiotherapy.  
  - Patients M0 who will receive radiotherapy and/or chemotherapy and no surgery.  
  - Patients with relapse M0 not candidates to surgery as the first therapeutic option. |
| Karnofsky ≥ 70 | Age > 18 years | Karnofsky ≥ 70 |

**EXCLUSION CRITERIA**

<table>
<thead>
<tr>
<th>HIGH GRADE GIOMA</th>
<th>RECTAL CANCER</th>
<th>PANCREATIC CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  - Dementia/psychiatric illness.  
  - Drug abusers (active in the last 5 years).  
  - mEHT treatment contraindicated.  
  - Another syncronic cancer.  
  - **No macroscopic disease**  
  - Another cancer diagnosed in the last 10 years. |  |  |
## CLINICAL STUDIES

<table>
<thead>
<tr>
<th></th>
<th>HIGH GRADE GLIOMA</th>
<th>RECTAL CANCER</th>
<th>PANCREATIC CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXTERNAL BEAM</strong></td>
<td>RT <strong>46Gy + 14 Gy Boost</strong></td>
<td><strong>45 Gy + 5.4Gy Boost</strong></td>
<td>36-54Gy (depending on the case)</td>
</tr>
<tr>
<td><strong>CHEMOTHERAPY</strong></td>
<td>Temozolamide</td>
<td>5-Fu / Capecitabine</td>
<td>Folinirinox / Gemcitabine / Platinum</td>
</tr>
</tbody>
</table>

### 2 STUDIES:

**1st study:**
- Patient candidates to standard RT-Chemotherapy
- Randomized
- 2 arms
  - **Arm 1:** Standard adjuvant RT-CT
  - **Arm 2:** Standard adjuvant RT-CT + mEHT (30 min before RT Monday-Friday)

**2nd study**
- Patient not suitable to any other standard oncological treat.
- 1 arm: mEHT only (3 times a week)

### 1 STUDY:

- Randomized
- 2 arms
  - **Arm 1:** Standard neoadjuvant RT-CT
  - **Arm 2:** Standard neoadjuvant RT-CT + mEHT (30 min before RT Monday-Friday)

### 1 STUDY:

- 1 arm, different groups:
  - Patients candidates to standard RT-CT + mEHT (30 min before RT Monday-Friday)
  - Patients not candidates to any standard treatment → mEHT (3 times a week)

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## COMMON POINTS FOR THE 3 STUDIES

### 6. TREATMENT DESCRIPTION.

**Treatment with modulated electrohyperthermia:**

- Patients will receive a treatment with modulated electrohyperthermia following the recommendations of the physician responsible for the study.

  - Patients who will receive concomitant radio and chemotherapy treatment:
    - mEHT treatment will be before each radiotherapy session.
    - Timing between the end of mEHT treatment and the beginning of radiotherapy treatment will be approximately 30 minutes. Before this 30 minutes, no patients will be treated with radiotherapy.
  
  - Patients who will receive mEHT treatment as an unique therapy:
    - mEHT treatment will be performed every 48 hours from Monday to Friday.
COMMON OBJECTIVES FOR 3 STUDIES

• **Main objectives:**
  - To evaluate the impact of performing a treatment with modulated electro hyperthermia, on the rates of **local, regional and distant control** in patients treated concomitantly with radio-chemotherapy, or as a unique treatment in those patients not candidates to standard therapies due to lack of efficacy or risk of toxicity as a single therapy.

• **Secondary objectives**
  - To analyze the impact of mEHT treatment (used concomitant with radio-chemotherapy or as a unique treatment) in the **cause specific and overall survival** rates, and **acute, subacute and chronic toxicities** from this treatment.
    - *For rectal cancer cases we will also evaluate:
      - The rates of sphincter preservation \(\rightarrow\) impact in QoL.
      - The rates of CR after neoadjuvant treatment.

HIGH GRADE GLIOMA STUDY: mEHTGlio

1.1 Title: “Treatment with modulated electro-hyperthermia in high grade gliomas (grade III and IV) as an adjuvant treatment to standard radiotherapy and chemotherapy or as a unique treatment”.

1.2 Protocol name: mEHTGlio

1.3 Date and protocol version: version 1.0 of May 20th 2018

1.4 Study/promotor:

Dra. Elisabeth Estafanía Arrojo Álvarez
Radiation Oncology department. University Hospital Marqués de Valdecilla
C/ Avenida Valdecilla s/n 39008 Santander
Email: gearrojo@hotmail.com
RECTAL CANCER STUDY: mEHTRec

1. GENERAL INFORMATION

1.1 Title: “Treatment with modulated electro-hyperthermia as a radio-chemosensitizer, in rectal cancer patients who will receive neoadjuvant standard long course radio-chemotherapy”.

1.2 Protocol name: mEHTRec

1.3 Date and protocol version: version 1.0 of May 20th 2018

1.4 Study promoter:

Dra. Elisabeth Estefania Arrojo Alvarez
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Email: eearrojo@hotmail.com

PANCREATIC CANCER STUDY: mEHTPan

1. GENERAL INFORMATION

1.1 Title: “Treatment with modulated electro-hyperthermia in locally advanced pancreatic cancer as radio-chemosensitizer, or as a unique treatment in patient not candidates to standard onco logical therapies”.

1.2 Protocol name: mEHTPan

1.3 Date and protocol version: version 1.0 of May 20th 2018

1.4 Study promoter:

Dra. Elisabeth Estefania Arrojo Alvarez
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C/ Avda. Valdecilla s/n 39008 Santander
Email: eearrojo@hotmail.com
RECRUITMENT AND LENGTH...

• **Expected recruitment:**
  • 60 cases each year for high grade gliomas.
  • 80 cases each year for rectal cancer
  • 30 cases each year for pancreatic cancer

• **Length of the studies:** 2 years.
  • Not a lot of time but....
  • **Results soon:**
    • High grade glioma  ➔ median survival around 12 months.
    • Rectal cancer  ➔ pre-surgery treatment, so response in surgical specimen.
    • Locally advanced pancreatic cancer  ➔ poor survival.

CONCLUSIONS

• The first* trials to analyze the **role of mEHT**
  applied as a radiosensitizer **30 minutes before**
  each radiotherapy session.
  • Up to date, in the published studies mEHT applied every 48 hours,
    not related with an “specific” timing with radiotherapy.
  • **Tumor oxygenation increases after mEHT, but how long do we**
    **have that “higher” oxygen levels?**
    • Maybe, if we treat every 48 hours, without a “timing relation” with
      radiotherapy, we loose that increase in radiosensitivity?
CONCLUSIONS

• Potencial advantages of adding mEHT to conventional oncological treatments.
  • Increase cancer cell killing
  • Increase radio-chemosensitivity → increase cancer cell killing
  • Not increase toxicities (more than 10.000 patients treated in clinical studies without significant toxicities with mEHT)
  • A potential to decrease toxicities.
    • Not curable tumors → cannot decrease current treatment "dose" at the moment.
    • Curable tumors → decrease treatment dose (for RT/chemo) → add mEHT → decrease toxicity → without risk in tumor control???

• For the future:
  • Other interesting studies: role of mEHT for microscopic disease.
    • Areas where RT treatment (conventional for this) is not possible. (ie. colon cancer).

THANK YOU!

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* All my efforts to all cancer patients, specially those so close to me...