Relation between Compliance and Response-Recurrence Rates in Head and Neck Tumors Treated with Hyperfractionated Thermo radiotherapy

Haim I. Bicher, M.D.¹

(1) Bicher Cancer Institute – 12099, W. Washington Blvd., #304 Los Angeles – Ca. 90066 - USA
Relation between Compliance and Response-Recurrence Rates in Head and Neck Tumors Treated with Hyperfractionated Thermo radiotherapy

Introduction
Hyperthermia, applied regionally, is a potent sensitizer of radiation therapy in the treatment of cancerous tumors and as such has been used as a palliation measure or more recently with curative intent. The ability of Hyperthermia to reoxygenate tumor tissue makes hypoxic tumors, such as sarcomas or glioblastomas more responsive to radiation. In a prior publication we discussed good therapeutic results (over 80% 5 years survival) using Hyperfractionated Thermoradiotherapy (HTRT) in heatable superficial tumors. In the current investigation we report on an expanded series of patients as well as performing a meta-analysis comparing HTRT with external beam radiation (EBRT) or chemoradiation.

Material and Methods
Hyperthermia was delivered using either Microwaves (BSD-100 or Cheng Laboratories) or Ultrasound (Labthermics) FDA approved equipment with appropriate applicators. Thermometry was done using microthermocouples placed in the tumor region (BCIW, LA, CA) for prostate tumors only ultrasound was used. Radiation was delivered by a 12 MEV Siemens Mevatron Machine adapted for IMRT and IGRT with a Lina-Tech system for computer planning and collimator alteration. Fractionation used involved daily hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180cGy to 100cGy resulting in the isoeffect biological equivalent dose lower by 15% to 25%, according to Ellis TDF formula. This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is adained, or failure determined. 40 breast patients, 27 head and neck and 22 prostate patients were treated with a follow-up of two to five years. All patients were early stage (III-a or less) the total dose is adapted to the clinical situation. To this effect, the use of objective end results parameters is introduced, including MRI, MR Spectroscopy, PET Scanning, Tumor Markers and PSA levels. Typically, the treatment is continued with further reduced doses until all the objective parameters confirm a complete response or failure is determined. Therefore, as opposed to classic radiation therapy, patients are treated to effect as objectively demonstrated, instead of to a pre-determined radiation does or number of fractions. Patient Population Patients included in this study belong to a subpopulation that refuses all standard medical treatments, including clinical radiation therapy, surgery and chemotherapy. All signed appropriate consent forms. The recruitment period was from January 1999 to July 2012.

Statistics
All test were done with Graph Pad Prism 4 sohware (Graph Pad Sohware Inc., San Diego, (USA) using the method of Kaplan and Meier. Meta-analysis was done by directly extrapolating published survival date for each type of tumor and comparing to current results with HTRT.

Results
1. Toxicity was minimal considering the biological equivalent of radiation doses given. Dermatitis and occasional thermal buns 6% of treatments, muscositis, thickness of saliva and altered taste during head and neck treatment. Hyperthermia did not seem to add to the radiation early effects. In all, the treatment was well tolerated on the vast majority of the patients. Side effects were less than with curative radiation therapy alone. No Grade IV toxicity (Common Toxicity Criteria) was observed.
2. Complete response rates were gratifying. Results of thermoradiotherapy confirmed our previous experience. Breast tumors, showed a compete response rate (CR) of 82%. The CR rate for head and neck tumors was 88% and for prostate tumors 93%. Meta-analysis comparing HTRT with conventional radiation shows a 30 to 50% advantage for HTRT in terms of 5-year survival and response rate. Survival rates with HTRT were around 80% warranting treating early superficial tumors with HTRT alone.

3. Projected 5 year survival was at a very high level for early stage head and neck cancer upwards of 80% (Figure 1) in compliant patients which compares well with radiation therapy alone or chemoradiation.

4. Comparison survival after treatment with HTRT versus chemo-radiation or EBRT (external beam radiation therapy). (Figure 1) depict the comparison in projected 5 years survival time between the 3 modalities (HTRT, EBRT and chemo-radiation).

![Graph showing survival rates](image)

**RT = Radiation Therapy, RT-CT = Chemo & Radiation, HTRT = Hyperfractionated Thermoradiotherapy**

*Figure 1. Percentage Survival Overtime Head and Neck Tumors – Callais, Q*

Patients that completed the projected course of (HTRT) maintained the high percentage of 5 year survival (88%). (Table 1)

<table>
<thead>
<tr>
<th># of Patient</th>
<th>Response</th>
<th>Recurrence</th>
<th>Dissemination</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Complete # [%]</td>
<td>5 [12]</td>
<td>5 [12]</td>
<td>40 [88]</td>
</tr>
</tbody>
</table>

*Table 1. The mechanism of ICD. The process of the DAMP formation, immune-recognition and immune-activation*

However patients that discontinued treatment before being medically discharged, the survival rate decreased to 20% (Table 2)

<table>
<thead>
<tr>
<th></th>
<th>Compliant</th>
<th>Non-Compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>88%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2. Survival Rate Compliant VS Non-Compliant*

**Discussion**

A method is designed to treat superficial heetable tumors of the head and neck with curative intent when at early, non-disseminated stages-Higher response and survival rates can be achieved with less, more moderate toxicities than with EBRT or chemoradiation, as shown by Meta analysis, therefore we reached the following tentative conclusions, which apply only to compliant patients that successfully completed the treatment course.
The New and the Old ONCOLOGY GOAL
OLD: DUMP and PRAY
• Give MAXIMUM DOSE of TOXIC TREATMENT MODALITY
• PRAY FOR RESULTS.

NEW:
• Use less toxic Thermoradiotherapy,
• TREAT to EFFECT, OBJECTIVELY DOCUMENTED

Conclusion
Protracted RT Hyperfractionation with daily Hyperthermia.
• Decreases the side effects of radiation therapy.
• Allows treating to effect using objective end point parameters (tumor markers, PET scans, MRI, etc.).
• Accomplishes a high percentage of complete responses in superficial tumors.
• Accomplishes a high 5-year survival rate in the 80-90thi range in early superficial tumors.
• Is potentially curative in early stage breast, head and neck and prostate cancers.
• Is more effective and less toxic than radiation or chemotherapy.

The Future of Hyperthermia
1. Treat with curative intent
2. Find a niche where Hyperthermia will be included in the guidelines for the NOVO therapy. Suggestions: Head and Neck, Prostate, Breast, Sarcomas
3. Became part of institutional tumor boards to implement these objectives and accrue patients
4. Emphasize proven palliative effectiveness of Hyperthermia. Specially pain palliation (eg. Bone, pain, chest, wall recurrences, etc.) Design prospective, randomize multi-institutional trials to prove points 1, 2 and 4.

Summary
HTRT as previously described (20) consist of daily Hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180cGy to 100cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. This decrease is compensated by the increase number of hyperthermia fractions which potentiates each dose. Treatment is continued until an objective complete response is adained, or failure determined. 45 head and neck patients were treated with a follow-up of two to five years. All patients were early stage (less than III). However a cohort of 12 patients were non-compliant and discontinued treatment after receiving at least 2/3 of the prescribed radiation dose.

Results
Complete responses were obtained in 88% in the compliant patient group- with 5 local recurrences and 5 cases of dissemination-the survival rate remains at 88%. In the non-compliant cohort complete responses were 20%, recurrences 11%, dissemination 80thi and survival 20%. Toxicity in both groups was equivalent. No grade IV side effects (common toxicity criteria) were observed.

Conclusion
Protracted hyperfractionation of daily thermoradiotherapy decreases the side effects of radiation therapy, allows treating to effect using objective and point parameters, accomplishes a high percentage of complete responses and a high 5-year survival rate in the 80-90% range in early head and neck tumors, where it can be considered as potentially curative. However compliance with the protracted regime is crucial to accomplish the desired results.