Oncothermia Journal 7:102-107 (2013)

Hyperfractinated thermoradiotherapy (HTRT) is more effective and less invasive than radiation or chemoradiation in heatable cancers – a meta analysis

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This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

Hyperfractinated thermoradiotherapy (HTRT) is more effective and less invasive than radiation or chemoradiation in heatable cancers – a meta analysis

Intruduction

It has been proven in malignant cancers, that in case of metastatic nodes in the head and neck region [1, 2, 3, 4, 5, 6] and in several other locations [8, 9, 10] hyperthermia potentiates radiation therapy. Due to these early findings, clinical applications were limited to recurrent advanced or metastatic cancers [11, 12, 13]. However, prospective randomized trials in the
1990's demonstrated the effectiveness of thermoradiotherapy not only in superficial tumors but also when deeper structures were affected [14, 15], provided these tumors could be effectively heated. The addition of heat roughly doubles the effectiveness of radiation, but also the fact that hyperthermia may increase tumor oxygenation [16, 17, 18] make hypoxic tumors such as sarcomas or glioblastomas more susceptible to thermoradiotherapy [19]. In previous publications [19, 20] we described a treatment regimen based on protractions of the radiation fractionation combined with daily hyperthermia treatment coinciding with each radiation dose. This regimen seems to be effective in eradicating tumors with diminished toxicity.
A remarkable projected 5-year survival rate was reported in the 80-90% of the region in to superficial heatable tumors (breast, head and neck and prostate) [20] In the current investigation we undertook update the current results as well as to perform a meta-analysis corresponding survival rates using HTRT with conventional radiation (EBRT) or chemo radiation.

Material and methods

Hyperthermia was delivered using either Microwaves (BSD-100 or Cheng Laboratories) or Ultrasound (Labthermics) FDA approved equipment with the appropriate applicators. Thermometry was done using micro-thermocouples 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. The daily doses of radiation are progressively decreased from 180cGy to 100cGy resulting in the isoeffect biological equivalent dose by 15% to 25%. According to Ellis TDF formula, (see Table 1.)

200 x 25 = 5,000	TDF = **82**	35 x 200 = 7,000	TDF = **115**
Protracted Hyperfractionation			
[cGy]	TDF	[cGy]	TDF
180 X 10 = 1800	28	180 X 10 = 1800	28
150 X 10 = 1500	21	150 X 10 = 1500	21
120 X 10 = 1200	15	120 X 10 = 1200	15
100 X 5 = 500	6	100 X 10 = 1000	11
		50 X 30 = 1500	12
35 Fx = 5000	**70**	70 Fx = 7000	**87**

Comparison of Radiation Bioligoical Effectiveness (TDS #) between Conventional and Protracted Fraction Regions.

Table 1. Radiation therapy fractionation conventional fractions

This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment was continued until an objective complete response was attained, 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 in early stage (III-a or less) the total dose was adapted to the clinical situation. To this effect, the use of objective end results parameters was introduced, including MRI, MR Spectroscopy [21], PET Scanning, Tumor Markers and PSA levels. Typically, the treatment was continued with further reduced doses until all the objective parameters confirmed a complete response or failure was determined. Therefore, as opposed to classic radiation therapy, patients were treated to effect as objectively demonstrated, instead of to a pre-determined radiation dose 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 2010.

Statistics

All tests were done with Graph Pad Prism 4 software (Graph Pad Software Inc., San Diego, (USA) using the method of Kaplan and Meier. Meta-analysis was done by directly extrapolating published survival date [28, 29, 30, 31] for each type of tumor and by comparing the current results with HTRT.

Results

1. Toxicity was minimal considering the biological equivalent of radiation doses given. Dermatitis and occasional thermal burns (61 % of treatments in breast patients); nausea, vomiting and occasional diarrhea and cystitis were experienced when treating pelvic fields in prostate patients; mucositis, thickness of saliva and altered taste were experienced during the 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. There were fewer side effects than with curative radiation therapy alone. No Grade IV toxicity (Common Toxicity Criteria was observed of note patients treated for prostate cancer exhibited less sexual dysfunction than it was reported after conventional radiation.
2. Complete response rates were gratifying results of thermoradiotherapy of or our previous experience [21-27]. Breast tumors, showed a complete response rate (CR) of 82%. The CR rate for head and neck tumors was 88% and for prostate tumors it was 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% warranted treating early superficial tumors with HTRT alone.
3. Projected 5-year survival in this updated series remain at a very high level for early stage breast head and neck and prostate tumors (see Figure 1.) (see Table 2.) upwards of 80%.

Head And Neck	88%
Prostate	87%
Breast	80%

Table 2. Five year overall survival rate

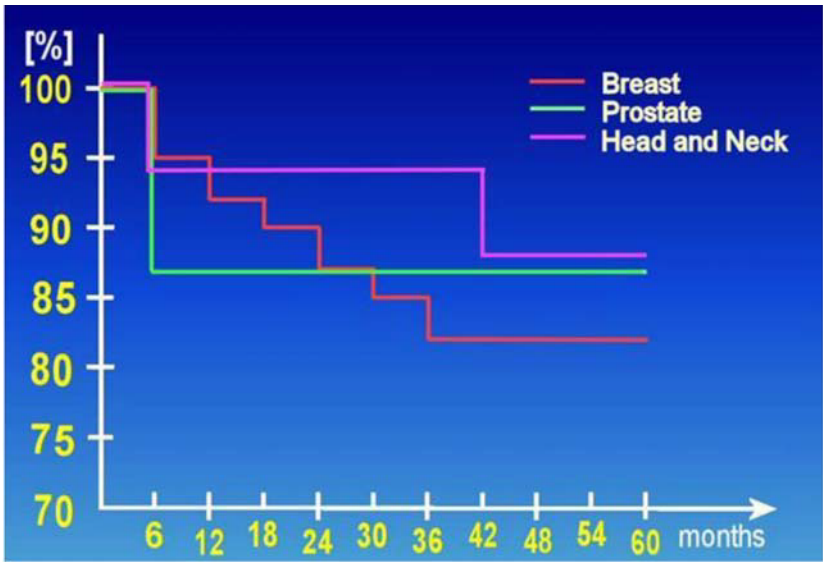

Figure 1. Percentage survival overtime breast, head ands neck, and prostate

4. Comparison survival after treatment with HTRT versus chemo-radiation or EBRT (external beam radiation therapy). (see Figures 2., 3., and 4.) depict the comparison in projected 5 years survival time between the 3 modalities (HTRT, EBRT and chemo-radiation)

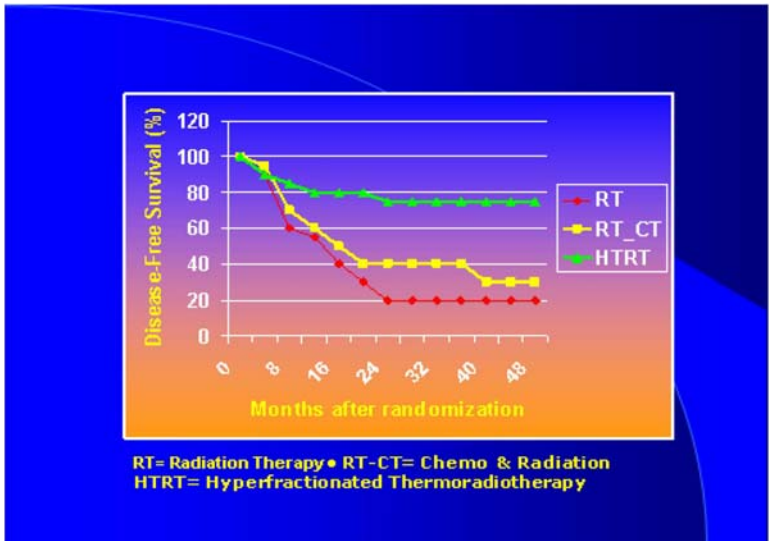

Figure 2. Percentage survival overtime head and neck tumors – Callais, Q [28]

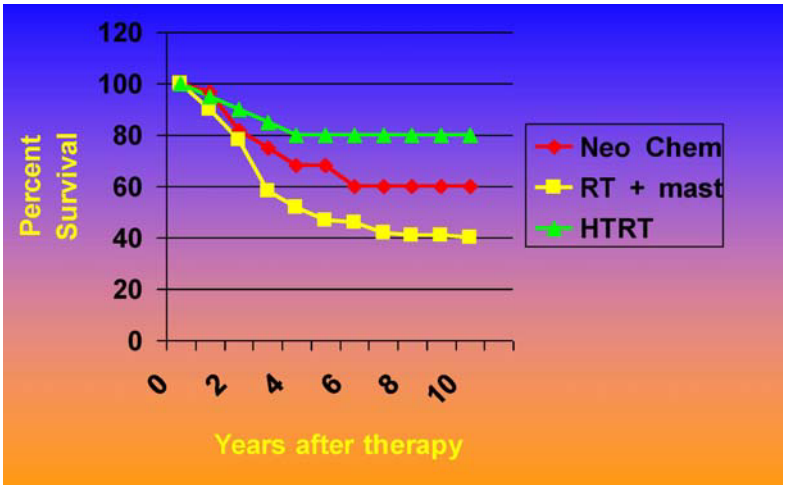

Figure 3. Percentage survival overtime breast tumors – Perez, C [29]

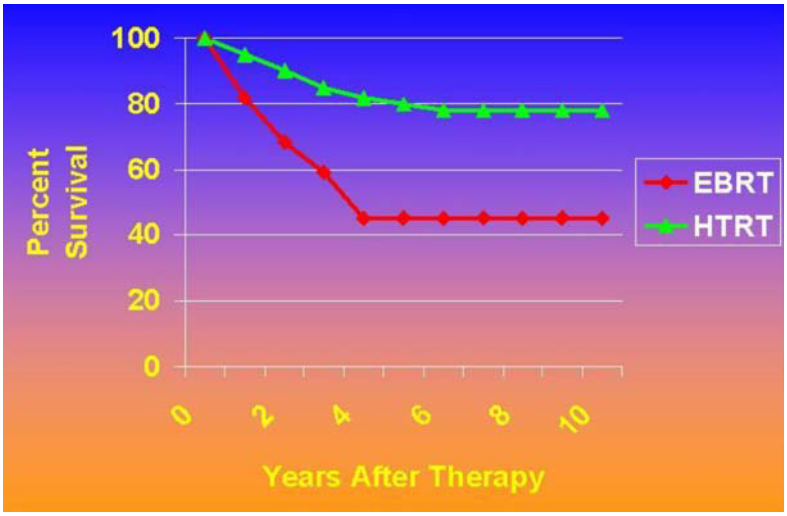

Figure 4. Percentage survival overtime prostate tumors – Perez C and Bradely [30]

In regard to treatment of disseminated prostate tumors, it should be noted that in patients able to obtain and maintain prior treatment, 90% could be treated without developing impotence, as compared with 50% that lost sexual ability when treated with EBRT, as depicted in Figure 5.

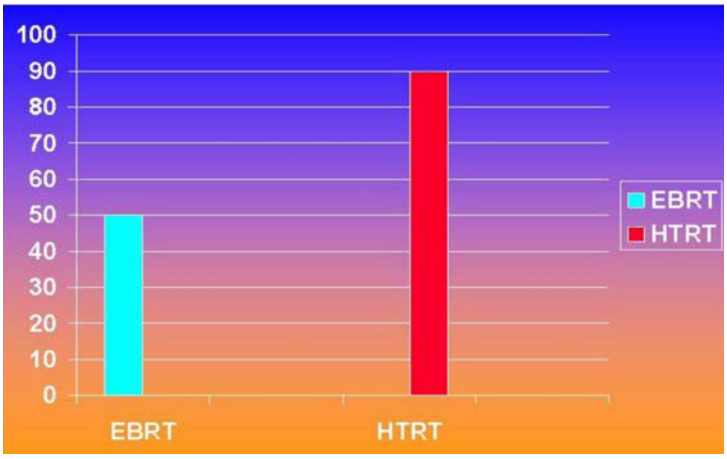

Figure 5. Percentage of patients able to obtain and maintain erection one year after treatment with HTRT and eBRT of prostate tumors – Siglin, A [31]

Discussion

A method is designed to treat superficial heatable tumors (head and neck, breast and prostate 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.

The new and the old new 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 hyperfraction with daily hyperthermia

- Decreases the radiation dose by 15 to 25%
- Decreases the side effects of radiation therapy
- Allows treating to effect using objective and 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 80-90% 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 guide lines for the NOVO therapy. Suggestions: Head and Neck, Prostate, Breast, Sarcomas
3. Become part of institutional tumor boards to implement these objectives and accrue patients.

4. Emphasize the proven palliative effectiveness of Hyperthermia. Especially pain palliation (eg. bone, pain, chest, wall recurrences, etc.) Design prospective, randomize multi-institutional trials to prove points 1, 2, and 4

Summary

HTRT consists of daily Hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180 to 100 cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. 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 attained, or failure is determined. 60 breast patients, 35 head and neck and 25 prostate patients were treated with a follow-up of two to five years. All patients were early stage (less than III).

Conflict of interest

The author declares no conflict of interest from the research plan and results with any commercial entity mentioned in the paper.

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