Conference Paper

Hyperfractionated Thermoradiotherapy Is More Effective and Less Invasive Than Radiation or Chemoradiation in Heatable Cancers: A Meta-Analysis

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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 determined. Sixty breast patients, 35 head and neck, and 25 prostate patients were treated with a followup of two to five years. All patients were early stage (less than III). HTRT proved to be less toxic and more effective than radiation or chemoradiation therapies.

1. Introduction

Hyperthermia, applied regionally, is a potent sensitizer of radiation therapy in the treatment of cancerous tumors [1–10] and as such has been used as a palliation measure [11–13] or more recently with curative intent [14]. The ability of Hyperthermia to reoxygenate tumor tissue makes hypoxic tumors, such as sarcomas or glioblastomas, more responsive to radiation [15]. In a prior publication [14], we discussed good therapeutic results (over 80% 5-year 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.

2. 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, and 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 LinaTech 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 180 cGy to 100 cGy 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 attained, or failure determined. Forty breast patients, 27 head and neck, and 22 prostate patients were treated with a followup 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 [16], PET scanning, tumor markers, and PSA levels. Typically,

TABLE 1: Five year overall survival rate.

Head and neck	88%
Prostate	87%
Breast	80%

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 predetermined radiation dose or number of fractions.

2.1. 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.

3. Statistics

All tests were done with Graph Pad Prism 4 software (Graph Pad Software Inc., San Diego, CA, USA) using the method of Kaplan and Meier. Meta-analysis was done by directly extrapolating published survival date [17–20] for each type of tumor and comparing to current results with HTRT.

4. 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 when treating pelvic fields in prostate patients; mucositis, 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. Of note patients treated for prostate cancer exhibited less sexual dysfunction than reported after conventional radiation.

(2) Complete response rates were gratifying. Results of thermoradiotherapy confirmed our previous experience [16, 21–26]. Breast tumors showed a complete 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 in this updated series remain at a very high level for early-stage breast head and neck and prostate tumors (Table 1) upwards of 80%.

(4) Comparison survival after treatment with HTRT versus chemoradiation or EBRT (external beam radiation therapy). Figures 1, 2 and 3 depict the comparison in projected

FIGURE 1: Percentage survival over time: head and neck tumors—Calais et al. [17]. RT= radiation therapy. RT-C = chemotherapy and radiation. HTRT = hyperfractionated thermo-radiotherapy.

FIGURE 2: Percentage survival over time: breast tumors—Perez et al. [18].

5-year survival time between the 3 modalities (HTRT, EBRT, and chemoradiation).

In regard to treatment of disseminated prostate tumors, it should be noted that in patients able to obtain and maintain erection prior to treatment, 90% were able to be treated

FIGURE 3: Percentage survival overtime prostate tumors—Perez and Bradley [19].

FIGURE 4: Percentage of patients able to obtain and maintain erection one year after treatment with HTRT and EBRT of prostate tumors—Siglin [20].

without developing impotence, as compared with 50% that lost ability when treated with EBRT, as depicted in Figure 4.

5. Discussion

A method is designed to treat superficial heatable tumors (head and neck, breast, and prostate with curative intent when at early, nondisseminated 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.

6. The New and the Old New Oncology Goal

Old: Dump and Pray.

- (i) Give maximum dose of toxic treatment modality.
- (ii) Pray for results.

NEW.

- (i) Use less toxic thermoradiotherapy
- (ii) Treat to effect, objectively documented.

7. Conclusion

Protracted RT hyperfractionation with daily hyperthermia

- (i) decreases the side effects of radiation therapy;
- (ii) allows treating to effect using objective endpoint parameters (tumor markers, PET scans, MRI, etc.);
- (iii) accomplishes a high percentage of complete responses in superficial tumors;
- (iv) accomplishes a high 5-year survival rate in the 80–90% range in early superficial tumors;
- (v) is potentially curative in early-stage breast, head and neck, and prostate cancers;
- (vi) is more effective and less toxic than radiation or chemotherapy.

8. The Future of Hyperthermia

- (1) Treating with curative intent.
- (2) Finding a niche where hyperthermia will be included in the guidelines for the NOVO therapy. Suggestions: head and neck, prostate, breast, and sarcomas.
- (3) Becoming part of institutional tumor boards to implement these objectives and accrue patients.
- (4) Emphasizing proven palliative effectiveness of hyperthermia, especially pain palliation (e.g. bone, pain, chest, wall recurrences, etc.). Designing prospective, randomize multi-institutional trials to prove points 1, 2, and 4.

Conflict of Interests

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

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