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Hyperthermia Combined With Radiation In Treatment Of Locally Advanced Prostate Cancer: Long-term Results Of DFCI 94-153

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Abstract

Background—A phase 2 study was done to assess efficacy of transrectal ultrasound hyperthermia with radiation +/− androgen suppression for treatment of locally advanced prostate cancer. Long-term results of this trial are now presented.

Methods—Patients with clinical T2b-T3b, N0, M0 disease (1992 AJCC criteria) received radiation plus 2 transrectal ultrasound hyperthermia treatments. Subsequent to the first 4 patients, 6 months of androgen suppression was allowed. The study was designed to assess absolute improvement in 2-year disease-free survival rate as compared with the short-term androgen suppression arm in RTOG 92-02.

Results—Thirty-seven patients received a total of 72 hyperthermia treatments. Mean CEM T90 43°C was 8.4 minutes. 1992 AJCC clinical stage: T2b 19, T2c 8, T3a 5, and T3b 5 patients. Median Gleason score was 7 (range, 6–9), and median PSA was 13.3 (2–65) ng/nl. Thirty-three patients received androgen suppression. With a median follow-up of 70 months (18–110 months) 7 year overall survival is 94% with 61% of patients failure free (ASTRO definition). Absolute rate of disease free survival at 2 years, the primary study endpoint, was significantly improved (84%) when compared with a rate of 64% for similar patients on the 4 month androgen suppression arm of RTOG 92-02. Using Phoenix criteria (PSA nadir +2) for biochemical failure, 89% of patients were failure free at 2 years.

Conclusions—Hyperthermia combined with radiation for treatment of locally advanced prostate cancer appears promising. Further study of hyperthermia in treatment of prostate cancer with optimal radiation and systemic therapies is warranted.

Keywords

hyperthermia; thermometry; prostate cancer; radiation therapy; androgen deprivation

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INTRODUCTION

The benefits of hyperthermia with radiation are widely recognized. The biologic rationale for combination of heat with radiation is compelling. Tumor cells most resistant to radiation, including those that are hypoxic, at low pH, nutritionally deprived, and in S phase, are precisely the cells most sensitive to hyperthermia.[1,2] Hyperthermia also enhances the effect of radiation through induction of apoptosis and other mechanisms of cell kill.[3,4,5] This theoretical benefit of hyperthermia has been shown to have meaningful clinical impact as evidenced by results of phase III trials including survival benefit.[6]

Technical challenges in treatment delivery, including difficulty achieving therapeutic temperatures for deep seated tumors, has hindered wide spread use of hyperthermia. Likewise, hyperthermia is often viewed as labor and time intensive, as many hyperthermia treatment regiments have required weekly or bi-weekly treatments over the course of radiation therapy.

A phase II study at the Dana-Farber Cancer Institute (DFCI 94–153) was initiated to provide a preliminary assessment of efficacy of transrectal ultrasound hyperthermia in combination with radiation and, for most patients, androgen suppression in treatment of intermediate to high risk clinically localized prostate cancer. The use of a transrectal applicator allows for direct energy deposition into the prostate to enhance tumor heating while minimizing thermal dose to surrounding normal tissues and organs, thus addressing the challenge of heating deep-seated pelvic organs. Use of the applicator assessed in this study was shown to be feasible and safe in a prior phase I study.[7,8] Building upon the treatment regimen applied in this earlier study which showed promising clinical results[8], the phase II trial incorporated only two hyperthermia treatments administered within the first four weeks of radiation therapy spaced at least a week apart to minimize any lingering thermal resistance from the initial treatment. We have previously reported the favorable toxicity profile of this treatment approach.[9] The long-term efficacy results of this completed trial are now presented.

METHODS

All patients were enrolled in a phase II study at the Dana-Farber Cancer Institute (DFCI), including men with clinical stage T2b-T3b, N0, M0 disease by 2002 AJCC criteria. The study was IRB approved and all patients provided informed consent. Staging for all patients included bone scan and CT of the abdomen and pelvis. Patients received 6660 cGy +/− 5% normalized to 95% (approximately 7000 cGy ICRU 38 reference dose) with 180–200cGy fractions. All patients were treated with an initial field inclusive of the prostate and seminal vesicles with 1.5cm margin followed by a prostate only boost with 1.5cm margin. Radiation therapy was administered with a four-field technique using ≥6 MV photons. Two hyperthermia treatments were administered at least one week apart during the first four weeks of radiation. Following accrual of the first four patients, an amendment was made to the protocol to allow for use of androgen suppressive therapy (AST) to reflect changes in the standard of care for many patients eligible for the study.[10,11,12] The recommended study regimen called for a total of six months of combined LHRH agonist with a non-steroidal anti-androgen, including two months of neo-adjuvant hormonal therapy before initiating radiation therapy. For patients receiving AST, simulation was typically performed prior to initiation of treatment.

Details of the transrectal hyperthermia system have been previously reported.[9] The ultrasound power was delivered from a water cooled 16 element partial-cylindrical intracavitary array. Power deposition was individually controlled for each of the 16 transducers and a closed heating/cooling system using degassed bolus water was used to

control the anterior rectal wall temperature. Patients were placed in the lateral decubitus position for treatment. Placement of interstitial temperature and perfusion probes was accomplished via a transperineal route using transrectal ultrasound guidance. Three Bowman probes were placed with one each in the right and left lateral peripheral zones approximately mid-point in anterior-posterior axis, and the third in the central posterior portion of the peripheral zone. During this portion of the procedure most patients received propofol, a short acting IV general anesthetic, supplemented with midazolam and fentanyl, while maintaining spontaneous ventilation. Once the probes were satisfactorily placed within the prostate the transrectal hyperthermia probe was introduced into the rectum. Patients were then allowed to return to an alert state, but at times received further light IV sedation, sufficient for communication of any pain, positional, or heat discomfort.

Power was then applied for a minimum goal of 60 minutes at therapeutic temperature as defined by attainment of a temperature of 42.0°C by at least one intra-prostatic temperature sensor or allowing for 10 minutes of initial heating. The thermal treatment goal was to achieve a cumulative equivalent minutes (CEM) T_{90}43°C of 10 minutes. This parameter is used to equate a range of actual temperatures achieved to a reference temperature (43°C). The temperature exceeded by 90% of the measured temperature points (T_{90}) when given over a period of time is converted to equivalent minutes (EM) at 43°C as defined by Sapareto and Dewey[7]. The CEM T_{90}43°C is the summation of the EMT_{90}43°C for each hyperthermia session over the course of treatment.

Temperature profiles were obtained for each thermocouple in 30 second intervals over the course of treatment. The maximum rectal wall temperature at any single point was limited to 40°C (19 patients), 41°C (3 patients), or 42°C (15 patients). The limitation of the rectal wall temperature to 40°C in the initial 19 patients hindered achievement of the thermal treatment goal for a majority of the patients since the applied power typically had to be reduced to keep the rectal wall temperature below 40°C. Since there was minimal rectal toxicity experienced with a rectal wall temperature limit of 40°C, the DFCI institutional review board allowed for an increase in allowable rectal wall temperature to 42°C in a step-wise manner with three patients first treated at 41°C. Once the session was completed all probes were removed and patients then received radiation within one hour of completion of hyperthermia.

The study was designed to have 80% power to detect a 20% absolute improvement in the two-year disease-free survival rate observed on the short-term androgen suppression arm in RTOG Trial 92-02, from 64% to 84%. Wilcoxon rank sum test was used to evaluate the differences in median CEM T_{90} 43°C for different groups, and differences in median duration of treatments for different treatment sessions. Overall survival and PSA failure free survival were estimated using the Kaplan-Meier method. A two-sided p-value less than or equal to 0.05 was considered statistically significant.

RESULTS

Thirty-seven patients received a total of 72 hyperthermia treatments between September, 1997 and April, 2002 on the DFCI phase II hyperthermia trial. Median follow-up was 70 months (range 18–110), median age was 64 (45 – 78) years, 1992 AJCC clinical stage T2b (19 patients), T2c (8 patients), T3a (5 patients), and T3b (5 patients). Median Gleason score was 7 (6–9), and median PSA was 13.3 (2–65) ng/nl. All patients completed conformal radiation therapy with CT treatment planning to a median dose of 6700 cGy (6340 – 7200 cGy) as normalized to 95%. Thirty-three patients received androgen suppressive therapy initiated within three months prior to radiation therapy. All but two of these patients received six months of AST, with one patient receiving nine months, and another twelve

months of AST. Amongst the first four study patients, all whom did not receive AST, only 1 patient failed at the primary study endpoint of 2 years with one additional patient failing with longer term follow-up.

Thirty-five of thirty-seven patients received two hyperthermia treatments. Median duration of treatment was 62.8 (39 – 80) minutes per treatment session and did not differ significantly between the first and second treatments. A favorable long-term toxicity profile noted with this treatment regimen was previously reported.[9] Temperature profiles are shown in Table 1. The mean CEM T_{90} 43°C for all 37 patients was 8.4 minutes. When assessed by allowable rectal wall temperature, those with a rectal wall maximum of ≤40°C had a mean CEM T_{90} 43°C of 5.6 minutes versus 11.4 minutes for patients with an allowable rectal wall temperature ≤42°C. A Wilcoxon rank sum test of the difference in median CEM T_{90} 43°C for these two groups, 2.8 minutes versus 10.5 minutes, was significant ($p = 0.004$). A small difference in disease free survival was noted in favor of the higher temperature group, however, it is noted that the study was not designed to assess impact of temperature on treatment outcome.

PSA failure was defined using the ASTRO consensus definition. The Phoenix definition of PSA failure, defined as nadir + 2ng/ml, was developed after the study was designed and while not part of the primary analysis was assessed as well to provide a basis for comparison with contemporary studies. In addition to the ASTRO definition of PSA failure, failure was also defined by clinical or pathologic evidence of local or distant disease recurrence, or at the time of initiation of salvage androgen suppression regardless of PSA. With a median follow-up of 70 months (18–110 months), overall survival was 94% (Table 2). At seven-year follow-up, 61% of patients were failure free applying the 1997 ASTRO consensus (Table 3), and 55% were failure free applying the nadir +2 definitions of biochemical failure (Table 4). Notably, the Kaplan-Meier curves for both overall and disease free survival appear to level off after five years, as can be seen in Figures 1 through 3. Three patients developed metastatic disease, of which one patient died of prostate cancer 30 months after treatment. Absolute rate of disease-free survival at two years, the primary study endpoint, was significantly improved with hyperthermia (84%) as compared with a rate of 64% for similar patients on the four month androgen suppression arm of RTOG 92-02 that served as the comparison group for this study. Using Phoenix criteria (nadir +2) for biochemical failure, 89% of patients were progression-free at two years.

DISCUSSION

The present study provides the longest follow-up reported to date for use of hyperthermia in treatment of prostate cancer administered on a prospective phase II trial. Prior studies have demonstrated that prostate hyperthermia can be safely and effectively administered using a variety of strategies for administration of heat.[9,14,15] In addition to the issues of safety and feasibility, others have shown potential benefit to use of hyperthermia in treatment of locally advanced prostate cancer.

In the earliest report of outcomes with prostate hyperthermia, Anscher et al assessed local-regional using an annular phased array radiofrequency device combined with a median dose of 6840 cGy external beam radiation in 21 patients with T2b-T4 or recurrent prostate cancer with median Gleason score of 7 and median PSA of 69. Five or ten hyperthermia treatments were planned. Three-year overall and disease free survival were 88% and 25% respectively. No significant increase in acute or long term toxicity with the addition of hyperthermia to radiation was noted. The only predictor of relapse was pre-treatment PSA.[13]

Deger et al reported promising early results with the use of interstitial hyperthermia with implanted self-regulating thermoseeds in 57 patients with T1-T3 prostate cancer (95% T2 or T3). Median pre-treatment PSA was 11.6 and median WHO grade was G2. Biochemical progression was defined by the ASTRO consensus definition. 6840 cGy in 180 cGy fractions was administered concurrent with six hyperthermia treatments with implanted 55°C Curie thermoseeds. Median follow-up was 36 months. Nine patients progressed at a median time of 20 months. Median PSA was 0.55ng/ml two years after therapy.[16]

Tilley et al reported results with 22 patients on a phase I//II trial treated with 6840 cGy and regional hyperthermia weekly for five to six weeks. Fifteen patients had primary T3pN0MO disease and seven had histologically confirmed local recurrence following radical prostatectomy. Five patients received short-term androgen suppressive therapy. PSA control was defined as a nadir of <1ng/ml. PSA progression according to the ASTRO consensus definition was defined for cases exceeding 2ng/ml and levels between 1–2ng/ml were also judged to be progression if PSA increased on two successive occasions. With median follow-up of six years, six-year relapse free survival was >50% for primary patients but no long-term control was noted for recurrent patients with six-year overall survival of 95% and 60% for primary and recurrent patients respectively. A clear correlation was found between higher temperatures and thermal doses with PSA control.[17]

Maluta et al reported on 144 patients with T3-T4, or T2 with Gleason ≥7 or PSA ≥10 prostate cancer treated with conformal radiation therapy to a mean dose of 7400 cGy with hyperthermia on a phase II trial. Androgen deprivation was administered to 64% of patients, with a high degree of variability in type and duration of treatment, lasting up to five years in some high-risk patients. Local-regional hyperthermia was administered with the BSD 2000 system weekly, up to a maximum of five treatments during radiation therapy. With median follow-up of 51.7 months, five-year biochemical disease free survival as defined by the ASTRO consensus definition was 49% and overall survival was 87%. Hyperthermia was well tolerated with no significant side effects noted.[18]

Algan et al reported on the long term results of a precursor phase I/II study assessing the transrectal ultrasound hyperthermia system used in our study. Twenty-six patients with high-risk prostate cancer (American Urologic Society Stage C2-D1, median PSA 29ng/ml) received a median dose of 6800 cGy with either one (9 patients) or two (17 patients) hyperthermia treatments. Biochemical failure was defined by the ASTRO consensus definition. The median follow-up was 71 months, and the overall and cause specific five-year survival rates were 73% and 79%, respectively. Median and five-year biochemical no evidence of disease (bNED) survival were 36 months and 35% respectively in this high-risk patient population. On multivariate analysis, a pre-treatment PSA of ≤ 10ng/ml was a significant predictor of bNED survival. The duration of hyperthermia therapy showed a trend toward significance for overall survival ($P = 0.06$).[8]

The current study provides further support to the hypothesis that hyperthermia may be beneficial in treatment of locally advanced prostate cancer. A significant benefit was noted with addition of hyperthermia in this patient population when compared prospectively with the study designated control group of patients treated on the short-term androgen suppression arm of RTOG 92-02. While the patients on RTOG 92-02 are in many ways similar to the patients eligible for this trial and were treated with similar radiation and AST parameters, only a phase III study can provide conclusive evidence of efficacy.

Since this study was initiated in the mid-1990's much has been learned about risk stratification. More stringent eligibility criteria identifying patients with bulky local disease but at relatively low risk of harboring micrometastases may aid in further defining the

benefit of hyperthermia in prostate cancer, as hyperthermia is unlikely to ultimately benefit patients with pre-existing sub-clinical distant disease.

The relatively modest radiation doses used in this study are now recognized as being associated with sub-optimal tumor eradication. An argument can be made that with current capabilities to safely dose escalate with radiation, hyperthermia is not necessary for treatment of prostate cancer. While such assertion may very well be true for a majority of patients, the use of very tight margins required with dose escalation may not be desirable for some patients with locally advanced disease. Additionally, there may be some patients who harbor relatively radioresistant tumor cells who could benefit from hyperthermia. Future developments in functional imaging and molecular profiling may lead to targeted selection of patients for complimentary treatments to radiation such as hyperthermia. Likewise patients for whom salvage radiation therapy is being considered after primary treatment may benefit from combined use of modest radiation doses with hyperthermia. As there are commercially available systems to administer hyperthermia for prostate cancer, the lessons learned from the present study continue to be relevant and applicable to current clinical scenarios.

The duration of AST remains a topic of controversy. While RTOG and EORTC trials have shown a significant survival advantage to 2–3 years of AST in high-risk patients,[12,19] others have shown survival advantage in intermediate to high-risk patients with 4–6 months of AST.[20,21] The full impact of different durations of hormonal therapy, including time periods intermediate between 4–6 months and 2–3 years, remain to be fully defined. As the use of long-term AST is associated with significant morbidities, the combination of radiation, hyperthermia, and short-term AST may be an attractive alternative for some patients with intermediate to high risk clinically localized prostate cancer.

Apart from traditional hyperthermia geared toward radiosensitization, thermal ablation for prostate cancer is gaining therapeutic momentum. There are significant challenges, however, in completely ablating the prostate without damage to the urethra, bladder, rectum, and neurovascular bundles. It is well recognized that there is a hyperthermic rim around the ablated tissue region. An attractive strategy may be to combine thermal ablation with modest doses of radiation. A safe margin for ablation near critical normal structures can be maintained taking advantage of the hyperthermic rim to sensitize tumor in these regions to eradication with radiation. The finding of enhanced benefit of hyperthermia with radiation doses used in this study support such approach. Indeed, the degree to which hyperthermia improved treatment outcome is similar to that seen with radiation dose escalation[22, 23] and comes without any added risks associated with higher radiation doses. The benefit seen in this phase II study also supports the hypothesis that the thermal enhancement ratio is significant for prostate cancer and worthy of further investigation.

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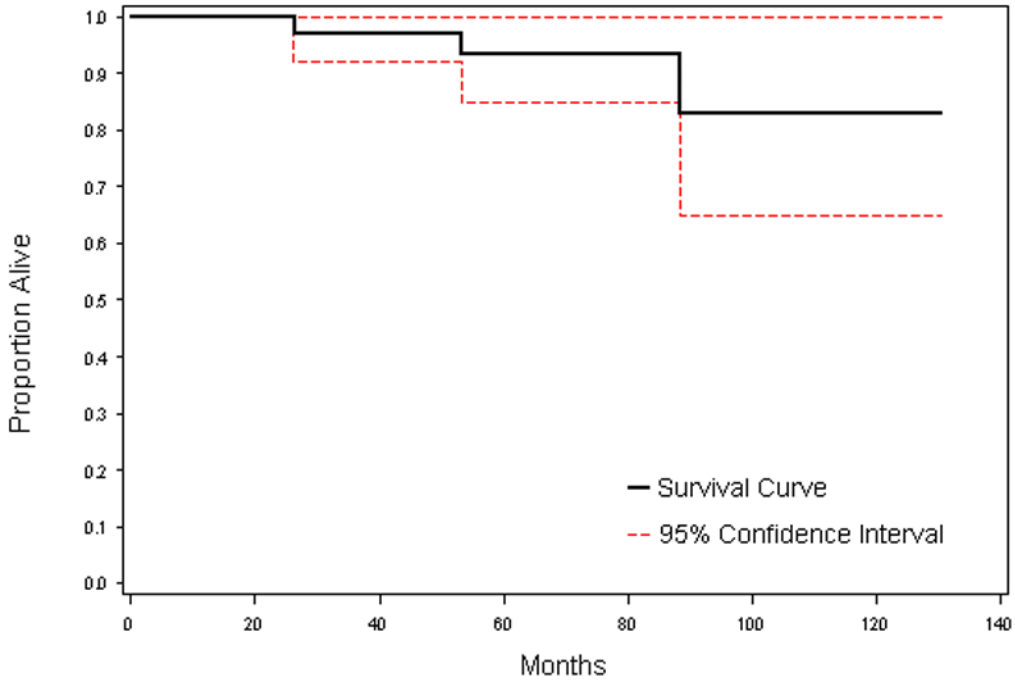

Figure 1.
Overall Survival

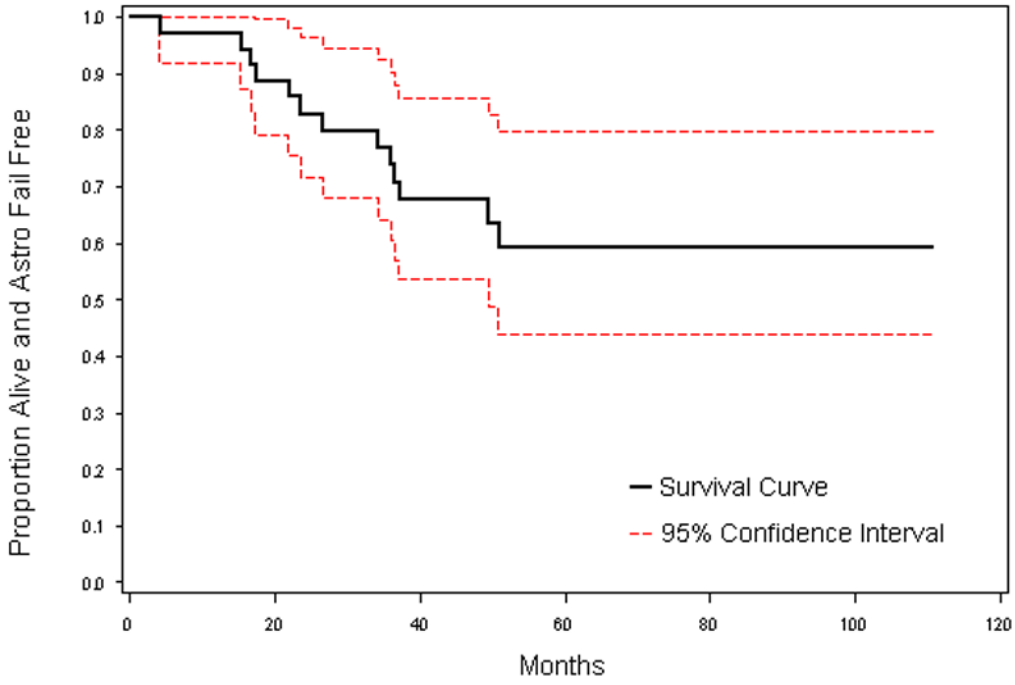

Figure 2.
ASTRO PSA Freedom From Failure

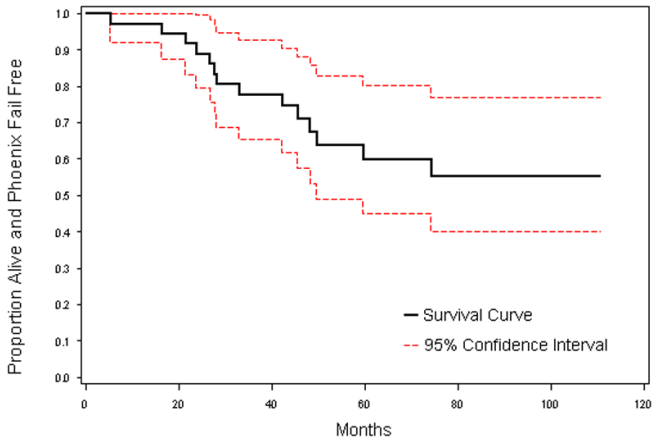

Figure 3.
Phoenix Definition (Nadir + 2) Freedom From Biochemical Failure

Table 1

Thermal Treatment Parameters

	Min	Max	Ave
Time	39.0min	80.0min	62.8 min
T min	37.5^0	41.8^0	40.1^0
T ave	39.2^0	42.8^0	41.2^0
Tmax	40.5^0	45.9^0	42.5^0
$EMT_{90}43$	0.1	21.9	4.3
$CEMT_{90}43$	0.4	27.2	8.4

Table 2

Overall Survival

Time	# of pts	# of Event	OS rate				
			2 yrs	4 yrs	5 yrs	6 yrs	7 yrs
OS months	37	3	100%	97.2%	93.5%	93.5%	93.5%

Table 3

ASTRO PSA Freedom From Failure

Time	# of pts	# of Event	AsFFS rate				
			2 yrs	4 yrs	5 yrs	6 yrs	7 yrs
Astro fail months	37	13	83.5%	68.7%	60.6%	60.6%	60.6%

Table 4

Phoenix Definition (Nadir + 2) Freedom From Biochemical Failure

Time	# of pts	# of Event	PhFFS rate				
			2 yrs	4 yrs	5 yrs	6 yrs	7 yrs
Phoenix fail months	37	14	89.0%	71.3%	60.0%	60.0%	55.4%