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HYPERTHERMIA AND RADIATION THERAPY FOR LOCALLY ADVANCED OR RECURRENT BREAST CANCER

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Abstract

Introduction—This study aims to report the outcome and toxicity of combined hyperthermia (HT) and radiation therapy (RT) in treatment of locally advanced or loco-regionally recurrent breast cancer.

Patients and Methods—Patients treated with HT and RT from January 1991 to December 2007 were reviewed. RT doses for previously irradiated patients were >40 Gy and for RT naïve patients >60 Gy, at 1.8–2 Gy/day. HT was planned for 2 sessions/week, immediately after RT, for a minimum of 20 minutes and for >4 sessions. Superficial or interstitial applicators were used with temperature measured by superficial or interstitial thermistors based on target thickness. HT treatment was assessed by thermal equivalent dose (TED), >42.5°C and >43°C. Endpoints included treatment response, lack of local progression (local control), and survival.

Results—127 patients received HT and RT to 167 sites. These included the intact breast (24.4%), chest wall/skin (67.7%), and breast/chest wall and nodes (7.9%). At a median follow-up

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of 13 months (mean 30 ± 38), improved overall survival was significantly associated with increasing RT dose ($p < 0.0001$), median TED 42.5°C 200 minutes ($p = 0.003$), and local control ($p = 0.0002$). Local control at last follow-up was seen in 55.1% of patients. Complete response was significantly associated with median TED 42.5°C 200 minutes ($p = 0.002$) and median TED 43°C 100 minutes ($p = 0.03$).

Conclusion—HT and RT are effective for locally advanced or recurrent breast cancer in patients that have been historically difficult to treat by RT alone. Over 50% of patients achieved control of locoregional disease. Overall survival was improved with local control.

Keywords

Hyperthermia; Radiation Therapy; Breast Cancer; locoregional recurrence; locally advanced; reirradiation; interstitial applicator

Introduction

Locally advanced or recurrent locoregional breast cancer can be difficult to control with a single treatment modality. Gross disease on the chest wall or breast, or in the regional nodes is often symptomatic and is often psychologically distressful to patients who observe their disease daily. Surgical resection alone is associated with a high risk of failure. Chemotherapy rarely results in complete response. High radiation therapy doses are required for control and can result in complications. Often, a combination of different modalities is used to increase response and duration of control.⁽¹⁾

One modality—hyperthermia—can potentiate the effect of radiation and has been shown to improve local control in patients with advanced breast cancer.^(2, 3) Hyperthermia refers to the artificial increase in tissue temperature to $40^\circ - 44^\circ\text{C}$. It is an effective cytotoxic agent in low-pH, hypoxic and nutrient deprived conditions, those that one finds in hypoxic regions of gross tumors. Radiation resistance is often observed in these same tumor regions. In addition, hyperthermia may potentiate RT effect as it may reduce tumor cell repair of sublethal RT-induced DNA damage and may increase tumor oxygenation through improved vasodilatation, blood flow, and a potential change in the tumor cell metabolism. Hyperthermia causes protein denaturation in the cells, which can lead to damage to all intracellular signaling pathways including DNA repair. Duration of HT and timing relative to RT are critical to observe potentiation of RT effect.^(4–7)

A number of randomized clinical studies have demonstrated the clinical benefit of combined HT and RT in various tumor sites.^(8–11) HT is an underused modality due to the number of available facilities, duration of treatment, difficulty measuring tumor temperature, number of experienced clinicians with the modality, and insurance reimbursement.

We report our clinical experience using hyperthermia and radiation therapy in patients with locally advanced and recurrent breast cancer. Tumor response, treatment outcomes, and adverse effects were evaluated.

Patients and methods

Patients Selection

Hyperthermia records were accessed to identify patients with breast cancer treated to the breast, chest wall, and/or regional lymph nodes with hyperthermia and RT from January 1991 to December 2007. Patients could be treated with palliative or curative intent. After obtaining institutional review board approval, medical records were retrospectively reviewed to determine response, local control, survival, and toxicity.

Radiation Therapy

For RT naïve patients, radiation therapy fields included any gross disease. The entire breast or chest wall were included; regional nodes were generally treated. Typical adjuvant radiation fields for locally advanced breast cancer were used. 50 Gy in 1.8–2 Gy fractions was prescribed to areas without gross disease and a minimum of 60 Gy prescribed to gross disease. Bolus was used when there was skin involvement. Interstitial RT boosts were used to improve dose homogeneity in appropriate patients. For previously treated patients, radiation fields included gross disease plus a margin. A minimum target dose of 40 Gy was planned at 1.8–2 Gy per fractions. Bolus was generally used.

Hyperthermia

HT was delivered twice per week, immediately after RT. A minimum of 4 sessions was planned. More than 1 HT site was treated if tumor extended beyond the diameter of the applicators. Either superficial applicators (MA-120, MA-100, MA-150, MA-201 manufactured by BSD corporation) or interstitial applicators were used and chosen based on estimated thickness and width of the tumor target. Multiple measurement sites were made in each treatment field and intra-tumor measurements made if allowed the ability to place intratumoral thermistors. The goal was to deliver an intra-tumor temperature of $>42.5^{\circ}\text{C}$ for a minimum of 20 minutes and for optimally for >45 minutes. Temperature and HT length could be limited by patient comfort and/or intolerance, including pain. Each HT treatment and the entire HT treatment course were assessed using the thermal equivalent dose (TED), defined as number of minutes at temperatures $>42.5^{\circ}\text{C}$ and 43°C . Since multiple sites of temperature measurement were made, the median TED was determined for each patient, for each treatment, and for the entire treatment course.

Other therapy

Patients received sequential or concurrent systemic therapy or hormonal therapy at the discretion of the treating physicians. Different schedules and types of therapy were used and could not be analyzed for effect. Surgery was not routinely scheduled; 2 patients had mastectomies and patients were treated after resection for positive margins.

Response Assessment

Complete response (CR) was defined by disappearance of tumor in the treatment site. Partial response (PR) was defined as a $>50\%$ decrease in tumor thickness by clinical assessment. Response was difficult to assess in patients with large, locally advanced breast cancers. For

this reason, freedom from local progression was reported. Local control (LC) was defined as lack of progression in the treated area after maximum response achieved after treatment. Treatment response and tumor status were assessed by the treating physicians (radiation oncology or medical oncology) and were reported regularly in the patients' charts. Toxicity in the RT and HT fields was categorized by the Common Terminology Criteria (CTC) for AEs, version 3.0. To assess the incidence of severity of complications and their resolution during follow-up, the worst chronic toxicities were reported. Toxicities were registered at each treatment check and at each follow-up visit. Toxicities were coded for telangiectasia, desquamation, ulceration, fibrosis, and abscess formation.

Statistical Analysis

Continuous variables were summarized as means, standard deviations, medians, and ranges and categorical variables were summarized as frequencies and percentages. Survival rates were estimated via the Kaplan-Meier method and median survival times were reported along with 95% confidence limit point estimates. Differences in survival times and local control between groups were assessed by the log-rank test. All analyses were conducted in SAS version 9.4. Overall survival (OS) was measured from the first radiation treatment to death as a result of any cause.

Results

127 female breast cancer patients treated with HT and RT were identified. The median age of patients is 56 years (range 32–106). The median follow-up is 13 months and mean follow-up is 30 months (range 0–182 mo) and includes one patient who died before her first follow-up. Characteristics of tumor in treatment sites are summarized in Table 1. Most patients (79.2%) were treated for recurrent breast cancer on the chest wall. 76% had disease >3 cm in size. 43% had received prior RT to the treatment site. 54.3% of the patients had distant metastases at the time of treatment.

Radiation therapy (RT)

Radiation therapy delivered is summarized in Table 2. Sixteen percent of patients could not achieve 40 Gy.

Chemotherapy

Most patients had been treated with prior chemotherapy. Type and schedule of chemotherapy were not readily available for analysis. Concurrent chemotherapy was used at the discretion of the treating radiation oncologist and medical oncologist. Overall, 56.7% of patients received chemotherapy. Cisplatin-based regimens were often used for potential RT potentiation; however further details about all regimens' exact dosing, treatment length, and drug combinations are not currently available to be reported.

Treatment Outcome

Treatment outcomes are detailed in Table (3). A CR during treatment was observed in 52.7% and a PR in 26.8%. A minor response was observed in 7.1% and 13.4% of patients showed no response or progressive disease. Two patients were treated by a salvage

mastectomy. CR was significantly higher among patients who received a total median TED 42.5°C 200 minutes ($p = 0.002$), and median TED 43°C 100 minutes ($p = 0.03$). Patients who initially presented with early stage (I and II) disease prior to progression of breast cancer requiring hyperthermia treatment had a higher rate of CR versus those patients who initially presented with advanced stages disease ($p = 0.002$). Patients who achieved a CR were more likely to exhibit freedom of progression (79.4%) at their last follow up ($p < 0.0001$). 55.1% of the patients had local control, at a median follow-up of 13 months and a mean follow-up of 30 months (range: 0–182, SD: 38 months). All 18 patients treated for microscopic disease were locally controlled. Notably, only one patient had “0” months of follow; this patient is included per the predetermined study design that incorporated outcomes of all breast cancer patients who received hyperthermia within the study period and per the inclusion criteria. All 18 patients treated for microscopic disease were locally controlled. Using Fisher’s exact test, there was no significant difference in CR among patients who had prior RT (42.5%) versus those who did not (61.1%) ($p = 0.49$) (Figure 2).

The median OS from treatment was 16 months (95% CI: 12–21 months), and the 1-year, 3-year, and 5-year OS were 58.35%, 29.59%, and 22.05%, respectively. Figure 3 shows OS in all patients, analyzed for radiation dose, hyperthermia dose, chemotherapy, and disease status. Overall survival was impacted significantly by local control, radiation dose, hyperthermia dose, and stage at first presentation. Table (4) lists the hazard ratios associated with risk of death. A microscopic disease, hyperthermia median TED 42.5°C, Radiation > 50Gy, and mastectomy resulted in statistical significant lower risk of death. Via a stepwise selection, another reduced multivariate model revealed that mastectomy (HR 0.622; 95% HR confidence limits 0.396–0.977; $p = 0.0392$), total radiation > 50 Gy (HR 0.360; 95% HR confidence limits 0.186–0.698; $p = 0.0025$), and a microscopic target (HR 0.306; 95% HR confidence limits 0.138–0.681; $p = 0.0037$) significantly decreased the risk of death. The median TED 42.5°C showed a trend towards decreasing the risk of death (HR 0.667; 95% HR confidence limits 0.431–1.033; $p = 0.0697$).

Table (3) includes treatment related adverse events. Grade 3–4 desquamation was the most commonly reported treatment-induced adverse event (24.4% of the patients). Ulceration, telangiectasia, and fibrosis were reported in 6.7%, 4.7%, and 6.3% of the patients respectively. One patient had abscess formation. Using Fisher’s exact test, there was no significant difference in Grade 3–4 adverse events among patients who had prior RT (43.8%) versus those who did not (46.3%) ($p = 0.86$) (Figure 2).

Discussion

Locally advanced and recurrent breast cancer is often a difficult problem facing clinicians, if surgical resection is not possible. Visible or palpable cancer often adds to emotional distress, especially if associated with odor, discharge, or bleeding. Locoregional control in these patients may improve survival, but will enhance quality of life. When good local therapy (including re-irradiation) and optimal systemic treatment are not enough for local control -- either due to extent of local disease or in case of recurrent disease -- more potent strategies are needed for tumor control. In such cases, it becomes impossible to ignore the historic success hyperthermia has with control of refractory lesions.⁽¹²⁾

The mechanism of hyperthermia induced cell killing and tumor regression has been extensively investigated and is likely multifaceted. In addition to direct cell injury from the increased temperature itself (thought to cause damage to critical cytoskeletal and membrane proteins), there is a potentiating effect on radiation therapy.^(4–7) This happens through multiple mechanisms. (1) There is better oxygenation of tumor cells due to increased blood flow. Additionally, there may also be a shift in tumor cell metabolism towards an anaerobic state. Together, both factors increase the amount of oxygen available for radiation induced oxygen-mediated damage (via reactive oxygen species) and prevent hypoxia-induced radioresistance.^(13–16) (2) There is inhibition of tumor cell DNA repair.^(17–19) Disabling the heat-sensitive DNA repair machinery prevents recovery from radiation-induced sublethal and potentially lethal damage, which enhances radiation induced cell kill. (3) Biologically the effects are complementary, yielding synergy when combined with radiotherapy in mechanism of tumor cell injury. Hyperthermia primarily damages proteins, causing cellular injury by denaturing critical cytoskeletal and membrane bound proteins. Also, this is mostly unaffected by oxygenation status or replicative activity. While radiation induced DNA damage is sometimes fully realized with next attempted mitotic activity, hyperthermia has no such cell-cycle limitation. It is as likely to damage both poorly and well differentiated cells and is as likely to injure a tumor cell in the relatively radioresistant S-phase of mitosis. Altogether, the synergy of the different mechanistic actions between the two techniques can cause more balanced tumor cell injury and cell kill, improving overall tumor control.

The clinical ability of improved tumor control with hyperthermia has been demonstrated in multiple sites of disease including breast cancer, head and neck cancer, cervical cancer, melanoma, and soft tissue sarcomas.⁽¹²⁾ After an initial randomized controlled trial failed to demonstrate significant benefit (but for which hyperthermia methodology and quality assurance were strongly questioned), a large international cooperative study reported the positive combined results of five randomized control trials (conducted by 4 collaborative groups) that assessed adding hyperthermia to radiation when treating locally advanced or recurrent breast cancer.⁽²⁰⁾ The combined outcomes of the cohort of 306 patients demonstrated a significant benefit (59% vs 41%, $p < 0.001$) in local control with the addition of hyperthermia, defined as the minimal intratumoral temperature of 43°C even though a significant portion of the study cohort did not meet this criterion.⁽²¹⁾ The benefit was most pronounced in patients who had a recurrence in previously irradiated areas (57% vs 31%, OR 4.7, 95% CI 2.4–9.5), which could limit the ability and extent of re-irradiation. Notably, complete response achieved through hyperthermia was more prolonged than if achieved via radiation alone.

A more recent randomized trial of mostly breast cancer patients included rigorous and objective thermal dosimetry to ensure a well-defined hyperthermia treatment arm. 109 patients were randomized to radiation or radiation plus hyperthermia. Patients treated with hyperthermia were planned for at least a dose of 10 cumulative equivalent minutes at 43°C for 90% of measured points. This was in addition to conventionally fractionated external beam radiation to a dose of 60–70Gy or 30–66Gy (median: 41Gy) if previously irradiated. The proportion of patients receiving systemic treatment at the time did not differ between both arms. The complete response rate was significantly higher in patients treated with hyperthermia as opposed to radiation alone – 66.1% vs 42.65. Local control was also more

durable with hyperthermia, 48% vs 25% at last follow-up or death. The odds ratio for CR was 2.7 (95% CI, 1.2 to 5.8; $p=0.20$) in the hyperthermia group. Previously irradiated patients showed the most pronounced benefit in local control (68% vs 24%), thereby suggesting that hyperthermia overcomes the limits of reduced dose in re-irradiation.⁽²⁾ Use of chemotherapy a sensitizer did not influence response. Notably, 55% of patients maintained freedom from local progression for the duration of their life.

This study confirms the findings of the study by Jones et al.⁽²⁾ We again demonstrate the utility of combining hyperthermia with radiation for achieving local control. The type of patients referred for hyperthermia in this series generally had difficult local disease to control with radiation and have been heavily treated with systemic therapy (examples, Figure 1). The OS illustrated in figure 3 and Table 3 suggests that survival is impacted by local control and local therapy. This study shows that quality of hyperthermia affects response – both temperature and duration of hyperthermia; the median TED 42.5°C and 43°C was higher in controlled patients and in patients with CR. The control rate in our series is in line with what has been reported by other modern series, despite the fact that patient selection (as opposed to randomization) might have prompted use of this technique for patients with the poorest clinician-predicted chance of local control (i.e. as opposed to radiation alone). Uniquely, our data are specific to women treated for breast cancer (either for a local recurrence or for advanced extent of disease) and in this scenario, add credence to the belief that durable local control might improve overall survival in this disease setting.

To our knowledge, our patient cohort comprises one of the largest modern series to-date, examining the use of hyperthermia in the setting of breast cancer. Most patients were approached aggressively. Moreover, with relatively preserved institutional technique and applicator usage among patients, our thermal dosimetric data objectively demonstrate that carefully applied (and measured) hyperthermia can benefit local control. The limitation of this study include it being a single institution retrospective study with a nonstandard approach to systemic treatment (with individualized treatment plans determined per patient suitability and physician preference); the exact details of dose, duration, regimen, etc. of this heterogeneous mix of regimens was not reported. We believe that studying the use of hyperthermia within the context of a controlled prospective clinical trial is required.

Hyperthermia is a well-studied but potentially under-utilized technique that can provide significant clinical benefit through the effects of improved local tumor control. It is known that hyperthermia complements radiation due (in part) to the fact that hyperthermia affects hypoxic and oxic cells equally (unlike radiation and chemotherapy) and because hyperthermia has different patterns of cell cycle toxicity than either radiation or many types of chemotherapy. In general, while the full mechanistic details of its actions are not completely understood, its synergistic addition in enhancing radiation-induced tumor cell kill has been well established. Much work has suggested but not established that hyperthermia may be denaturing DNA repair proteins and therefore acts to prevent DNA repair following treatment with DNA-damaging chemotherapy and radiation. With continued investigation into specific clinical roles and more widespread adoption of its usage, it can continue to establish itself as a powerful oncologic tool. In addition, as new tools become available to deliver hypothermia through the use of heat-labile liposomes and

heat-delivering nanomaterials, use of hyperthermia coupled with radiation and chemotherapy may become more important in the anti-cancer therapeutic arsenal.^(22–24)

Conclusion

Hyperthermia and radiation therapy is an effective combination in obtaining local control in a group of patients that have been historically difficult to treat by radiation. Overall survival was related to the ability to obtain local control, higher doses of radiation, and higher doses of hyperthermia.

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Figure (1).

(1-a) Patient A – locally advanced breast cancer, (1-b) Patient A – hyperthermia applicators insertion, (1-c) Patient A at 3 years of follow up, (2-a) Patient B – locally recurrent breast cancer, (2-b) Patient B – hyperthermia applicators insertion, (2-c) Patient B at 6 months of follow up.

Figure (2). Percentage of complete response (A) and Grade 3–4 treatment induced adverse events (B) in all patients, those who did not have prior RT, and those who did have prior RT.

Figure (3).

Overall Survival (OS) curves for all patients and stratified by stage at first presentation, local control, Radiation Therapy (RT dose), Median TED 42.5°C, Median TED 43°C, chemotherapy, and primary versus recurrent tumor.

Table (1)

Tumor's characteristics:

Characteristics		N	%
Tumor			
	Primary	26	20.5
	Recurrent	101	79.5
Distant disease at presentation			
	Yes	69	54.3
	No	58	45.7
Time to recurrence			
	> 2 years	49	48.5
	2 years	52	51.5
Tumor Stage at first presentation			
	I	14	11.0
	II	51	40.2
	III	34	26.7
	IV	18	14.2
	N/A	10	7.9
Recurrence site			
	Breast	31	24.4
	Chest Wall/Skin	86	67.7
	Chest Wall/ Breast and lymph nodes	10	7.9
Prior RT			
	Yes	54	42.5
	No	73	57.5
Target size			
	Extensive (>3 cm)	96	75.6
	Gross (<3 cm)	13	10.2
	Microscopic (positive margins)	18	14.2

Table (2)

Treatment

Radiation therapy		N	%
	16 – 39.9 Gy	20	15.7
	40 – 50 Gy	53	41.7
	> 50 Gy	54	42.5
Original Surgery			
	Biopsy only	24	18.9
	Breast conservative surgery	29	22.8
	Mastectomy	74	58.3
Chemotherapy			
	Yes	72	56.7
	No	55	43.3
Interstitial hyperthermia			
	Yes	31	24.4
	No	96	75.6
Hyperthermia sites			
	1–2	122	96
	3–4	2	1.6
	5–6	1	0.8
	N/A	2	1.6
Applicators			
	MA-100	25	19.7
	MA-120	69	54.3
	MA-150	5	3.9
	Combined applicators / others	28	22
Number of measurements sites			
	< 5	11	8.7
	5 – 10	110	86.6
	> 10	2	1.6
	N/A	4	3.1
		In Minutes Median (range)	
Median TED 42.5°C			
	In all patients	208 (3, 910)	
	In controlled patients	257 (3,788)	
	In uncontrolled patients	193 (10,910)	
Median TED 43°C			
	In all patients	130 (2, 856)	
	In controlled patients	157 (2,494)	

Radiation therapy		N	%
	In uncontrolled patients	120 (7,856)	

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Table (3)

Treatment outcomes

		N	%
Treatment response			
	CR	67	52.7
	PR	34	26.8
	Minor response	9	7.1
	No Response	15	11.8
	Progressive disease	2	1.6
Freedom from local progression			
	Yes	70	55.1
	No	55	43.3
	N/A (mastectomy)	2	1.6
Overall Survival (OS) all patients *		In months (95% CI)	
	Median OS duration	16 (12, 21)	
	1-years OS rate (%)	58.35% (48.94%, 66.63%)	
	2-years OS rate (%)	40.09% (31.05%, 48.95%)	
	3-years OS rate (%)	29.59% (21.37%, 38.25%)	
	5-years OS rate (%)	22.05% (14.65%, 30.43%)	
Median OS stratified by tumor status at the time of hyperthermia treatment			
p = 0.27	Primary tumor	14 (8,16)	
	Recurrent tumor	21 (12,28)	
Median OS stratified by radiation therapy (RT) dose			
p < 0.0001	RT <40Gy	5 (1,20)	
	RT 40–50Gy	12 (8,19)	
	RT >50Gy	28 (16,52)	
Median OS stratified by initial stage at first presentation			
p = 0.005	I	26 (8,110)	
	II	16 (8,33)	
	III	22 (11,47)	
	IV	13 (2,16)	
Median OS stratified by Median TED 42.5°C			
p = 0.003	Median TED 42.5°C < 200	12 (5,21)	
	Median TED 42.5°C ≥ 200	21 (15,41)	
Median OS stratified by Median TED 43°C			
p = 0.09	Median TED 43°C < 100	12 (10,21)	
	Median TED 43°C ≥ 100	27 (15,41)	

		N	%
Median OS stratified by local control			
p = 0.0002	Local Control	22 (16,40)	
	No Local Control	9 (5,15)	
Complete response		%	
Complete response (% among patients with various initial stages at first presentation)			
p = 0.002	I	64.3%	
	II	56.9%	
	III	58.8%	
	IV	11.1%	
Complete response (% among patients with and without median TED 42.5°C 200 minutes)			
p = 0.002	Median TED 42.5°C < 200 minutes	34.7%	
	Median TED 42.5°C 200 minutes	64.1%	
Complete response (% among patients with and without median TED 43°C 100 minutes)			
p = 0.03	Median TED 43°C < 100 minutes	37.5%	
	Median TED 43°C 100 minutes	64.6%	
Complete response (% among patients who did or did not receive chemotherapy)			
p = 0.99	Chemotherapy	51.6%	
	No chemotherapy	51.5%	
Complete response (% among patients with and without local control)			
P < 0.0001	Local Control	79.4%	
	No Local Control	18.9%	

* Survival rates were estimated via the Kaplan-Meier method and median survival times were reported along with 95% confidence limit point estimates. Univariate analysis and comparisons between groups were conducted using the long-rank test, with a p-value of 0.05 indicating significance.

Table (4)

Multivariate analysis for the association between risk of death and various patient's, tumor's, and treatment's characteristics:

Parameter	Hazard Ratio *	95% Hazard Ratio Confidence Limits		p-value
Age	0.993	0.970	1.016	0.5389
Recurrent disease	0.456	0.115	1.800	0.2620
Time to recurrence < / >2 years	0.840	0.449	1.568	0.5833
Chest wall only vs. nodal disease	1.489	0.434	5.108	0.5267
Breast vs. nodal disease	0.889	0.230	3.435	0.8644
Mastectomy	0.399	0.194	0.820	0.0124
Total Radiation: 40–50 Gy	0.791	0.382	1.636	0.5271
Total Radiation: > 50 Gy	0.402	0.174	0.927	0.0326
Number of treatment sites = 3,4	2.309	0.431	12.366	0.3283
Number of treatment sites = 5,6	0.955	0.105	8.707	0.9677
Target size: Gross	0.448	0.180	1.113	0.0839
Target size: Microscopic (positive margins)	0.260	0.103	0.655	0.0043
Median TED 42.5°C	0.426	0.229	0.793	0.0071
Median TED 43°C	1.459	0.722	2.947	0.2923

* A hazard ratio less than 1 indicates a decrease in risk and a hazard ratio greater than 1 indicates an increase in risk