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● *Clinical Investigation*

SURVIVAL BENEFIT OF HYPERTHERMIA IN A PROSPECTIVE RANDOMIZED TRIAL OF BRACHYTHERAPY BOOST ± HYPERTHERMIA FOR GLIOBLASTOMA MULTIFORME

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Purpose: To determine if adjuvant interstitial hyperthermia (HT) significantly improves survival of patients with glioblastoma undergoing brachytherapy boost after conventional radiotherapy.

Methods and Materials: Adults with newly-diagnosed, focal, supratentorial glioblastoma ≤ 5 cm in diameter were registered postoperatively on a Phase II/III randomized trial and treated with partial brain radiotherapy to 59.4 Gy with oral hydroxyurea. Those patients whose tumor was still implantable after teletherapy were randomized to brachytherapy boost (60 Gy at 0.40–0.60 Gy/h) ± HT for 30 min immediately before and after brachytherapy. Time to progression (TTP) and survival from date of diagnosis were estimated using the Kaplan–Meier method.

Results: From 1990 to 1995, 112 eligible patients were entered in the trial. Patient ages ranged from 21–78 years (median, 54 years) and KPS ranged from 70–100 (median, 90). Most commonly due to tumor progression or patient refusal, 33 patients were never randomized. Of the patients, 39 were randomized to brachytherapy ("no heat") and 40 to brachytherapy + HT ("heat"). By intent to treat, TTP and survival were significantly longer for "heat" than "no heat" ($p = 0.04$ and $p = 0.04$). For the 33 "no heat" patients and 35 "heat" patients who underwent brachytherapy boost, TTP and survival were significantly longer for "heat" than "no heat" ($p = 0.045$ and $p = 0.02$, respectively; median survival 85 weeks vs. 76 weeks; 2-year survival 31% vs. 15%). A multivariate analysis for these 68 patients adjusting for age and KPS showed that improved survival was significantly associated with randomization to "heat" ($p = 0.008$; hazard ratio 0.51). There were no Grade 5 toxicities, 2 Grade 4 toxicities (1 on each arm), and 7 Grade 3 toxicities (1 on "no heat" and 6 on the "heat" arm).

Conclusion: Adjuvant interstitial brain HT, given before and after brachytherapy boost, after conventional radiotherapy significantly improves survival of patients with focal glioblastoma, with acceptable toxicity. © **1998 Elsevier Science Inc.**

Brain neoplasms, Glioblastoma multiforme, Radiotherapy, Brachytherapy, Hyperthermia, Microwave, ^{125}Iodine.

INTRODUCTION

Glioblastomas are very aggressive brain tumors that carry a poor prognosis, with a median survival of about 12 months. One technique that has been used to try to improve survival has been brachytherapy boost after conventional radiotherapy to give a very high focal dose while sparing surrounding normal brain tissue. At the University of California, San Francisco (UCSF), brain brachytherapy has been performed using high-activity ^{125}iodine sources since late 1979. The low energy of ^{125}iodine reduces radiation exposure to medical personnel and the high activity permits treatment at dose rates of 0.30–0.70 Gy/h, appropriate for treating rapidly dividing malignant glioma cells. Promising results have been obtained in patients with focal primary glioblastoma treated with brachytherapy boost after conventional radio-

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therapy, with median survival times of 18–19 months in two large series (30, 35). Although part of this apparent improvement in survival is undoubtedly due to patient selection, a recently completed multi-institutional, prospective, randomized trial (Brain Tumor Cooperative Group trial 8701) showed a significant survival benefit for brachytherapy boost in patients with primary malignant glioma ($p < 0.05$) (23). Despite this very aggressive treatment, local and marginal disease progression continue to be the most common patterns of failure after brain brachytherapy (1, 25, 35). A retrospective review of 97 glioblastoma patients treated at UCSF showed that higher brachytherapy boost dose was significantly associated with improved freedom from local tumor progression, but there was a trend toward worse survival for minimum brachytherapy tumor doses above about 50 Gy, probably due to excessive radiation necrosis (27). It is clear that strategies are needed to improve local and regional control without increasing radiation toxicity.

Hyperthermia (HT) (the elevation of tissue temperature to at least 41°C) kills cells as a function of time and temperature, inhibits repair of sublethal and potentially lethal radiation damage, and is particularly effective against cells that tend to be resistant to radiation (those in the S phase of the cell cycle and nutrient-deprived, low pH hypoxic cells) (3). Hyperthermia may also induce tumor reoxygenation, increasing radiosensitivity (13).

Because the threshold for thermal damage in normal brain tissue is only about 40–60 min at 42–42.5°C or 10–30 min at 43°C (24), most investigators have tried to heat brain tumors selectively (22). Previous Phase I/II HT trials performed at Dartmouth, the University of Arizona, and UCSF in patients with primary or recurrent brain tumors demonstrated that toxicity was acceptable and that selective brain-tumor heating was feasible using carefully controlled interstitial heat sources within stereotactically implanted catheters (18, 26, 28, 31). Also, a retrospective comparison of brachytherapy ± HT reported by Stea *et al.* suggested a benefit of adjuvant HT in patients with primary or recurrent Grade III or Grade IV gliomas. The median survival from the date of diagnosis was 35.1 months in patients who had HT vs. 22.3 months in those who had not had HT (32).

These nonrandomized studies laid the groundwork for the protocol reported here, a prospective, randomized trial for primary glioblastomas comparing brachytherapy boost ± interstitial HT (Brain Tumor Research Center 6G-90-2).

METHODS AND MATERIALS

Patient eligibility

Patients eligible for the protocol were nonpregnant adults at least 18 years old with a Karnofsky performance score (KPS) of at least 70, ability to give informed consent, and a primary supratentorial glioblastoma multiforme deemed suitable for interstitial brachytherapy. Tumors had to be unifocal, circumscribed, and ≤ 5 cm in diameter, without involvement of the sylvian fissure and without evidence of corpus callosum, ventricular, or subependymal spread on the postoperative computed tomography (CT) scan or magnetic resonance imaging (MRI). Laboratory eligibility criteria included blood urea nitrogen ≤ 30 mg% or creatinine ≤ 1.5 mg%, white blood cell count ≥ 4000/mm^3, platelet count ≥ 125,000/mm^3, total bilirubin ≤ 1.2 mg%, aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT) ≤ twice the upper limit of normal, and alkaline phosphatase ≤ twice the upper limit of normal.

No prior cytotoxic chemotherapy or radiotherapy was permitted. After study entry, operative reports were obtained and initial surgical procedures were classified as biopsy (removal of < 10% of the tumor), subtotal resection (STR; removal of 10–90% of the tumor), or gross total resection (GTR; removal of more than 90% of the tumor). Also, histological slides were obtained for review by a UCSF neuropathologist.

External beam radiotherapy

Radiation therapy was to begin within 4 weeks after surgery. Partial brain external-beam radiotherapy fields were to encompass the contrast-enhancing tumor with a 2–3 cm margin, treating with daily fractions of 1.8 Gy to a total dose of 59.4 Gy. During external-beam radiotherapy, patients were to take oral hydroxyurea (HU) as a radiosensitizer at 300 mg/m^2 every 6 h on Mondays, Wednesdays, and Fridays. A repeat CT or MRI scan was performed at the end of radiotherapy. If the tumor was still deemed to be implantable, the patient was then randomized to either brachytherapy alone ("no heat") or brachytherapy plus HT ("heat").

Interstitial brachytherapy

Brachytherapy was to be performed within 2 weeks after completion of external-beam radiotherapy. On the morning of the implant procedure, a stereotactic base ring[1] was fixed to the patient's head using local anesthesia and contiguous 3-mm thick contrast-enhanced CT scans were obtained through the tumor region with a localizing system mounted on the base ring. Using customized treatment-planning software (34), the target volume was outlined on each axial CT image just outside the edge of contrast enhancement, and an arrangement of implant catheters and sources was planned iteratively on a treatment-planning computer[2] to encompass the target volume with a 0.40–0.60 Gy/h isodose contour, conforming as closely as possible to the shape of the target volume. Typically, there were 2–6 catheters, each of which contained 2 to 3 high-activity ^{125}iodine sources ranging

[1] Brown-Roberts-Wells, Radionics, Burlington, MA.
[2] VAX 11-780 or VAX 4000 Model 300, Digital Equipment Corporation, Maynard, MA.

from about 10 to 20 mCi in activity. After approval of the plan by the radiation oncologist and neurosurgeon, the patient was taken to the operating room for stereotactic implantation of 2.5-mm diameter silastic afterloading catheters through 3.4-mm diameter skull twist drill holes using local anesthesia. The implant technique has been described in detail elsewhere (12, 28). The silastic catheters were glued to silastic collars that were sutured to the scalp. Sterilized nylon catheters containing the radioactive sources were then inserted within the afterloading catheters and a surgical clip was placed to hold the inner catheter in place within each outer silastic catheter. Orthogonal radiographs were taken with a fiducial marker box mounted on the base ring to allow verification of actual source positions and calculation of actual isodose contours. After delivery of 60 Gy at the prescribed isodose contour, catheters were removed at the bedside and the small scalp wound at each implant site was sutured closed. Patients were observed overnight before discharge to home.

Interstitial hyperthermia

Patients randomized to receive HT had dummy sources rather than actual ^{125}iodine sources afterloaded into brain implant catheters and verified with orthogonal radiographs on the day of catheter placement. The following morning, the patient was transported to the HT suite. Surgical clips on the implant catheters were carefully removed and the dummy sources within nylon inner catheters were withdrawn and replaced with sterilized helical-coil microwave antennas (20). These antennas consisted of miniature flexible coaxial cable modified to generate fairly uniform predetermined power deposition patterns ranging from 1.1–4.0 cm in length, extending to the antenna tip. Antennas were spaced 1.2–1.8 cm apart from each other within about 3–5 mm inside the edge of the target volume. One or two of the silastic catheters at the center and/or edge of the target volume were dedicated for monitoring temperatures continuously during HT, using at least one multisensor fiberoptic thermometry probe. Power at 915 MHz was applied and manually controlled to achieve steady-state temperatures within 5–15 min and then to maintain these temperatures for 30 min, heating as much of the tumor as possible to at least 42.5°C without exceeding a temperature of 50°C in the target volume or 44°C in normal tissue. Temperature probes were mapped at least every 10 min along the catheter to provide temperature data at 0.5-cm spatial increments along the thermometry catheter(s). After HT, the antennas and thermometry probes were removed and sterilized brachytherapy sources were afterloaded. After completion of brachytherapy, the ^{125}iodine sources were removed in the HT suite and HT was repeated, again heating for 30 min after achieving steady-state temperatures. The time interval between HT and brachytherapy was generally 15–30 min.

Further management and follow-up

No adjuvant chemotherapy was given on this protocol. Corticosteroids were prescribed as needed and tapered or discontinued whenever possible in patients who were stable or improving. Following brachytherapy ± HT, patients were followed with contrast CT or MRI brain imaging studies, neurological examination, and assessment of KPS every 2 months for 1 year, every 3 months the following year, and then every 4–6 months. Positron emission tomography (PET) and/or magnetic resonance spectroscopy scans were commonly obtained to help distinguish between tumor progression and radiation necrosis. Reoperation was generally recommended when there was clinical deterioration and/or steroid dependency with an enlarging contrast-enhancing lesion with surrounding mass effect and edema. A variety of salvage chemotherapy regimens were used in the event of tumor progression and, in selected cases, brachytherapy or radiosurgery was used as salvage therapy.

Tumor progression was coded as local or separate. Local tumor progression was scored when follow-up imaging showed significant (approximately 25% or more) increase in the volume of the contrast-enhancing lesion contiguous with and within 2 cm of the edge of the contrast-enhancing mass on the brachytherapy preplanning CT scan, unless reoperation and/or PET scans showed necrosis only or predominantly necrosis, and the lesion went on to stabilize or improve off therapy. Any new site of contrast-enhancement separate from the original tumor was scored as separate failure.

Thermal dose calculation

The time-temperature distributions in tumor achieved with the heat sessions were evaluated retrospectively by calculating the cumulative T_{90} and T_{50} thermal doses, parameters that are thought to be most predictive of treatment outcome (10, 14). During the course of therapy, temperature data were recorded continuously at 5–10-s intervals using fiberoptic temperature sensors. Depending upon the number of thermometry catheters and insertion lengths, multisensor (with 0.5- or 1.0-cm spaced sensors) and/or single sensors were positioned within the catheters. For brief periods during therapy, the sensors were moved from their stationary positions and used to "map" the temperature profiles in 0.5 cm increments along the catheters, approximately every 10 min. To perform the thermal dose analysis, continuous time-temperature curves were generated for each map position along the thermometry catheter(s) using an interpolation scheme that tracked the temperature changes of adjacent stationary points by using weighted averaging of the differential temperatures. Temperature readings taken while the thermometry probes were being mapped were edited out by linearly interpolating temperature across each map interval. Then the temperatures for each spatial point in tumor were averaged over each 1-min time-period, sorted among all other tumor temperature points for that time-period, and used to linearly interpolate the temperatures that 90% and 50% of the tumor points attained over that 1-min interval. These two temperatures were converted into T_{90} and T_{50} thermal doses in terms of equivalent minutes at 43°C (EM43°) using the formula

Table 1. Reasons for failure to proceed to randomization

Reason	Number of patients
Tumor progression noted postradiotherapy	11
Tumor progressed during radiotherapy	7
Patient refused brachytherapy or randomization	5
Insurance company refused to agree to randomization	2
KPS deteriorated to < 70 during radiotherapy	2
Patient deteriorated and refused to complete radiotherapy	2
Patient had early death from PE or hemorrhage	2
Patient inadvertently not randomized (had brachytherapy)	1
Technically not implantable (too close to orbit)	1
Total	33

$$\text{EM } 43° = t \cdot R^{(43-T)} \quad (1)$$

where t is the 1-min time at temperature T and the constant $R = 0.5$ for temperatures $\geq 43°C$ and R = 0.25 below 43°C (19). The cumulative equivalent minutes at 43°C for T_{90} and T_{50} (CEM 43°T_{90} and CEM 43°T_{50}) for each patient were obtained by summing up the corresponding thermal doses for each minute of both HT treatment sessions. Thermal dose was also calculated for each monitored point within the tumor to provide site-specific minimum and maximum thermal dose (CEM 43°T_{min} and CEM 43°T_{max}).

Statistical methods

Survival was the primary endpoint of the study. The study was designed to have a 90% power of detecting a 2-fold difference in median survival, based on a 1-tailed hypothesis test that required 37 patients per arm. Survival and time to progression (TTP) were measured from the date of diagnosis until the date of last follow-up or the date of death or tumor progression, respectively. Estimates of TTP and survival were computed using the method of Kaplan and Meier (8). Survival curves were compared with the log-rank test using a 1-tailed p-value consistent with the study design (11). The Cox proportional hazards model was used to allow analyses adjusting for patient age and KPS at study entry (2).

Toxicities were scored as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (fatal). Incidence rates of Grade 3 or higher toxicity were compared for implanted patients on the two treatment arms using a 1-tailed Fisher's Exact test.

RESULTS

Patient characteristics

From August 1990 through August 1995, a total of 118 patients were entered in the trial, of whom 112 were eligible. Reasons for ineligibility included wrong pathological diagnosis after UCSF review (5 cases) and technically non-implantable tumor (1 case). All 112 eligible patients had supratentorial, lobar glioblastomas except for one thalamic tumor. Overall, patient age ranged from 21–78 years (median, 54 years) and KPS ranged from 70–100 (median, 90). There were 74 males and 38 females.

Treatment

Type of initial surgical resection was coded as biopsy in 7 patients, subtotal resection in 64, and gross total resection in 41. Overall, 99 patients (88%) received an external beam radiotherapy dose of 59–60 Gy. Seven patients had lower doses (9.0, 15.0, 30.6, 50.4, 58.0, 58.2, and 58.7 Gy) and 6 patients had higher doses (61.2, 61.2, 65.8, 66.0, 70.0, and 71.4 Gy). Among the 79 randomized patients, external-beam radiotherapy dosage ranged from 58.2–65.8 Gy, with only 2 patients receiving less than 59 Gy and only 2 patients receiving greater than 60 Gy. Adjuvant oral HU was given with external beam radiotherapy in 111 of 112 eligible patients and in all 79 randomized patients, although it was discontinued early in 2 cases after skin rashes developed.

Of the 112 eligible patients, 33 enrolled on the trial were not randomized, most commonly due to tumor progression during external beam radiotherapy (7 patients), tumor progression noted on the repeat scan at the completion of radiotherapy (11 patients), or patient refusal to undergo brachytherapy or randomization (5 patients) (see Table 1). Of the eligible patients, 39 were randomized to "no heat" and 40 to "heat". Patient and treatment parameters for all eligible randomized patients are shown in Table 2. For a variety of reasons (shown in Table 3), not all randomized

Table 2. Patient and treatment parameters for 79 eligible, randomized patients

Parameter	"No heat" arm (n = 39) range (median)	"Heat" arm (n = 40) range (median)
Patient age (years)	21–75 (55)	24–73 (55)
KPS at study entry	70–100 (90)	70–100 (90)
Extent of resection		
Biopsy	2	2
Subtotal resection	19	24
Gross total resection	18	14
External-beam radiotherapy dose (Gy)	58.2–65.8 (59.4)	58.7–61.2 (59.4)

Table 3. Reasons for inevaluability or failure to proceed with assigned treatment

Treatment arm, problem, reason	Number of patients
"No heat" arm—no brachytherapy	
Tumor progression noted after randomization	2
No target on preplanning CT scan	1
Had pulmonary embolus after randomization	1
Allergy to CT contrast; problems with CT/MRI merge; had radiosurgery instead	1
Brachytherapy aborted due to bleeding; had radiosurgery instead	1
"Heat" arm—no brachytherapy	
Tumor progression noted after randomization	3
Head too large for stereotactic frame	1
"Heat" arm—brachytherapy, but no hyperthermia	
Tumor too close to sylvian fissure to allow geometry for HT	1
Decreased consciousness after implant procedure	1
Patient not cooperative enough with awake procedure	1
Patient refused hyperthermia	1
"Heat"—inevaluable	
Later review of external-beam radiotherapy portals showed that tumor bed had not been completely encompassed	1

patients underwent brachytherapy or HT per protocol. For the 69 randomized patients who did undergo brachytherapy ± HT, age, KPS, external-beam radiotherapy, and brachytherapy parameters were comparable for both arms, except that more catheters were placed in HT patients because of the need for dedicated thermometry catheters (Table 4).

A total of 32 "heat" patients underwent HT, one of whom was later found to be inevaluable for survival and TTP analyses because review of the teletherapy portals showed incomplete coverage of the tumor bed. These 32 patients had a total of 56 HT treatments; 8 patients had only one HT treatment, rather than two treatments, because of toxicity from the first treatment. With mapping of thermometry probes every 0.5 cm in one or two dedicated thermometry catheters, the number of tumor loci monitored ranged from 2–10 (median, 5). Hyperthermia treatment parameters are shown in Table 4 to help characterize the thermal doses achieved in this trial. The CEM 43°T_{90} ranged from 0–771 (median 14.1) equivalent minutes and CEM 43°T_{50} ranged from 0.1–4652 (median 74.6) equivalent minutes.

Salvage therapies were well balanced between the two arms for the 79 eligible, randomized patients as well as the 69 randomized, implanted patients. Among the 68 evaluable, implanted patients, salvage therapy was given to 19 of 33 "no heat" and 20 of 35 "heat" patients, including chemotherapy alone in 14 vs. 16 patients, chemotherapy and radiosurgery in 3 vs. 2 patients, chemotherapy and brachytherapy in 1 "no heat" patient, chemotherapy and external beam radiotherapy in 1 "heat" patient, and radiosurgery alone in 1 "no heat" patient and 1 "heat" patient.

Reoperation

Of 33 implanted "no heat" patients, 19 (58%) underwent 23 reoperations and 25 (69%) of 36 implanted "heat" patients underwent 35 reoperations, with 1–3 reoperations per patient. The date of the first reoperation ranged from 13–126 weeks after brachytherapy (median, 32 weeks) for "no heat" and 14–169 weeks after brachytherapy (median, 45 weeks) for the "heat" arm. Histopathologic findings for the "no heat" and "heat" arms were interpreted as necrosis only in 26% and 29% of cases, tumor and necrosis in 48% and 51%, and tumor only in 26% and 20%, respectively.

Time to progression

Of 112 eligible patients, 107 failed, 4 have not failed and 1 died without sufficient information to determine TTP. The

Table 4. Brachytherapy/HT parameters for 69 randomized, implanted patients

Parameter	"No heat" arm (n = 33) range (median)	"Heat" arm (n = 36) range (median)
Prescribed brachytherapy dose (Gy)	52.9–66.1 (60.1)	49.0–62.2 (60.2)
Prescribed brachytherapy dose rate (Gy/h)	0.35–0.65 (0.45)	0.37–0.83 (0.45)
Minimum brachytherapy dose (Gy)	26.1–66.8 (39.5)	15.5–54.0 (43.6)
Target volume (ml)	1.2–74.7 (9.7)	3.2–33.9 (12.1)
Volume encompassed in prescribed isodose line	3.6–95.7 (19.1)	4.3–46.8 (19.2)
Number of brachytherapy catheters	1–6 (3)	2–9 (5)
Number of ^{125}iodine sources	2–17 (7)	3–17 (10)
Total ^{125}iodine activity (mCi)	31–336 (102)	39–175 (99)
Number of tumor temperatures monitored	–	2–10 (5)
Number of heating antennas	–	1–7 (4)
CEM 43°T_{90}*	–	0–771 (14.1)
CEM 43°T_{50}*	–	0.1–4,652 (74.6)
Site-specific CEM 43°T_{min}*	–	0–675 (6.0)
Site-specific CEM 43°T_{max}*	–	1.2–12,509 (194)

HT = hyperthermia; CEM 43° = cumulative equivalent min at 43°C; T_{90} = temperature attained by 90% of tumor temperatures; T_{50} = median tumor temperature; T_{min} = minimum tumor temperature; T_{max} = maximum tumor temperature.

* Data given for 52 hyperthermia treatments in 30 "heat" patients (data not available for 2 heated patients; 4 patients on the "heat" arm not heated).

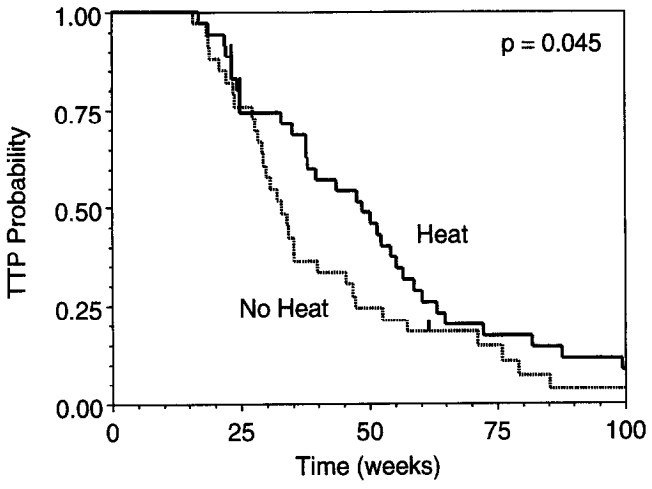

Fig. 1. Kaplan–Meier time to progression (TTP) curves for evaluable patients who actually had brachytherapy boost comparing 33 "no heat" patients to 35 "heat" patients (log rank $p = 0.045$). The median TTP was 33 weeks for the "no heat" group vs. 49 weeks for the "heat" group.

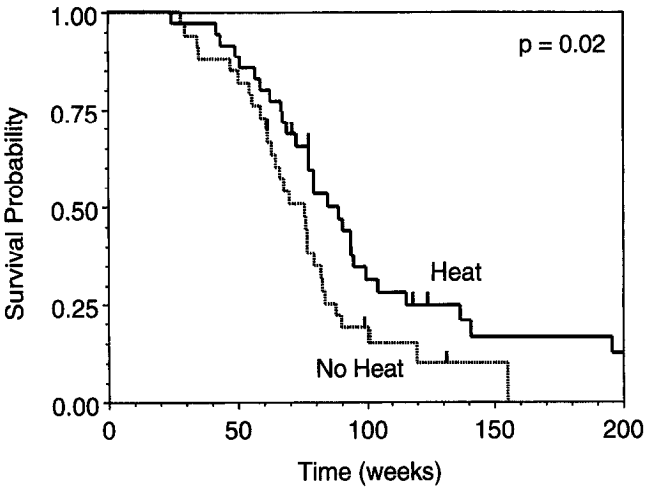

Fig. 2. Kaplan–Meier survival curves for evaluable patients who actually had brachytherapy boost, comparing 33 "no heat" patients to 35 "heat" patients (log rank $p = 0.02$). The median survival was 76 weeks for "no heat" patients vs. 85 weeks for "heat" patients with 2-year survival probabilities of 15% vs. 31%, respectively.

median TTP was 30 weeks for all 112 patients. Analysis of the 68 evaluable, implanted patients, showed that the median TTP was 33 weeks for "no heat" vs. 49 weeks for "heat" (Fig. 1; log rank $p = 0.045$; multivariate analysis $p = 0.043$). As the first sign of progression, separate failure without local tumor progression occurred in 4 (13%) of 31 "no heat" failures and 8 (24%) of 33 "heat" failures. The median time to local tumor progression was 35 weeks for "no heat" vs. 57 weeks for "heat" (log rank $p = 0.017$).

Survival

At the time of this analysis, 11 eligible patients were still living, all randomized, with follow-up ranging from 62 to 297 weeks (median, 117 weeks). Overall, the median survival was 67 weeks for all 112 eligible patients. Comparing the 39 eligible, randomized "no heat" patients to 40 "heat" patients (including the 1 inevaluable "heat" patient), the median survival times were 76 weeks for "no heat" vs. 80 weeks for "heat" (log rank $p = 0.04$; Table 5). Considering only the randomized patients who actually had brachytherapy and were evaluable, the median survival times were 76 weeks for 33 "no heat" patients (95% confidence interval 64–82 weeks) vs. 85 weeks for 35 "heat" patients (95% confidence interval 73–100 weeks) (Fig. 2; log rank $p = 0.02$), with mean survival times of 84 vs. 118 weeks and 2-year survival times of 15% vs. 31%.

A multivariate analysis of the 68 eligible, evaluable implanted patients to evaluate the influence of treatment arm ("heat" vs. "no heat") on survival, adjusting for patient age and KPS at the time of study entry, yielded a p-value of 0.008 for treatment arm with a hazard ratio of 0.51 favoring "heat" (Table 5), confirming a significant benefit of adjuvant interstitial HT in this protocol.

Although this study was not designed to look for a thermal dose-response relationship, we did retrospectively analyze this, as other investigators have done (9, 10, 14). Among the 30 "heat" patients with available thermal dose data, multivariate analyses of survival and TTP adjusting for age and KPS failed to show any meaningful thermal dose–response relationship for either CEM $43°T_{90}$ or CEM $43°T_{50}$ (comparing three thermal dose strata, <10, 10–50, and >50 equivalent min for CEM $43°T_{90}$ and <50, 50–250, and >250 equivalent min for CEM $43°T_{50}$). The CEM $43°T_{90}$ and CEM $43°T_{50}$ categorizations placed most of the patients in the same dose groups (low, medium, or high). Therefore, the predictive abilities of the two measures were similar, and we are unable to comment on which thermal dose parameter may be more predictive of survival or TTP.

Table 5. Univariate and multivariate analysis of influence of treatment arm on survival

Treatment group, parameter	Univariate	Multivariate*
All randomized patients ($n = 79$)		
p value	0.04	0.022
Hazard ratio (95% confidence interval)	0.65 (0.40–1.06)	0.60 (0.36–0.98)
Evaluable randomized, implanted patients ($n = 68$)		
p value	0.02	0.008
Hazard ratio (95% confidence interval)	0.58 (0.34–0.99)	0.51 (0.30–0.88)

* Adjusting for patient age and KPS.

Table 6. Brachytherapy/hyperthermia toxicities for 69 randomized, implanted patients

Toxicity grade and type	Number on "no heat" arm	Number on "heat" arm
Grade 1		
Neurological changes (mild or subjective changes)	1	7
Seizures (single partial seizure lasting ≤ 5 min)	3	6
Nausea/vomiting (able to eat, 1 episode/24 h)	1	2
Leukopenia (WBC 3000–3900/mm^3)	4	2
Grade 2		
Neurological changes (mild objective changes; normal function)	1	10
Seizures (partial seizure lasting > 5 min)	0	1
Nausea/vomiting (decreased intake, 2–5 episodes/24 h)	0	1
Fever without infection (38.1–40.0°C)	2	0
Leukopenia (WBC 2000–2900/mm^3)	1	0
Grade 3		
Neurological changes (objective findings & impaired function)	0	2
Generalized seizure	0	1
Implant site infection	0	1
Meningitis	0	2
Pneumonia	1	0
Grade 4		
Meningitis	1	1

Toxicity

Treatment toxicities during the course of external beam radiotherapy were generally mild and expected. There were no Grade 4 or Grade 5 toxicities, and only 2 Grade 3 toxicities, including 1 case of painful stomatitis so that a patient was unable to eat for a period of time and 1 case of hepatotoxicity from HU with elevation of liver enzymes to 9 times the upper limit of normal, resolving after stopping HU for 1 week and then resuming HU at a reduced dose.

Treatment toxicities during and within 30 days after brachytherapy ± hyperthermia are shown in Table 6. There were no Grade 5 toxicities on either treatment arm. There were 2 Grade 4 (life-threatening) cases of meningitis, including one on "no heat" and one on the "heat" arm. There was 1 Grade 3 toxicity (pneumonia) on "no heat" vs. 6 Grade 3 toxicities on "heat", including 2 cases of neurological changes impairing function, 1 generalized seizure, 1 implant site infection, and 2 cases of nonlife-threatening meningitis. Of note, 2 of the 6 Grade 3 toxicities on the "heat" arm occurred in patients who did not undergo HT, including 1 patient with decreased consciousness following the implant procedure (who was later found to have meningitis) and 1 patient who was not cooperative enough with the awake implant procedure and later developed an implant site infection. A Fisher's exact test comparing the incidence of serious (Grade 3 or higher) toxicities showed a trend toward more toxicities for "heat" than for "no heat" (1-tailed $p = 0.08$). Also of note is the higher incidence of Grade 1 and Grade 2 neurological changes and seizures for "heat" than for "no heat" (Table 6).

DISCUSSION

Multiple nonrandomized clinical studies in the 1970s and 1980s in patients with superficial advanced or recurrent squamous cell carcinoma, adenocarcinoma, and melanoma showed that the addition of HT to radiation tended to improve the tumor response rate (15, 29). In studies comparing results for paired lesions in the same patient, complete response (CR) rates averaged 31% for radiation alone vs. 71% for radiation plus HT (29). However, an early prospective, randomized trial in North America failed to show a benefit of adjuvant HT for superficial malignancies, most likely because tumor heating was inadequate except for tumors <3 cm diameter (17). Another prospective, randomized Phase III trial failed to show a benefit of adjuvant interstitial HT in combination with brachytherapy in 173 advanced or recurrent extracranial tumors, but only 1 patient met minimal criteria for an "adequate" HT session (5). These trials did result in the development of quality-assurance guidelines for superficial and interstitial HT procedures (4, 6). More recently, two European prospective, randomized trials showed improved local control of superficial malignancies (recurrent breast cancer and metastatic melanoma) treated with radiotherapy plus HT vs. radiotherapy alone (16, 33).

The trial reported here represents the first prospective, randomized trial in North America to show a local control or survival benefit for hyperthermia. Among 68 evaluable patients who actually had a brachytherapy boost ± HT, the HT arm had significantly improved TTP (median, 49 weeks vs. 33 weeks; $p = 0.045$) and significantly improved survival (median survival, 85 weeks vs. 76 weeks; 2-year survival 31% vs. 15%; $p = 0.02$). By happenstance, the median survival difference between the "heat" and "no heat" arms was not a very good descriptor of the difference between the two curves, which, for example, was 94 vs. 77 weeks at the 40% probability level and 116 vs. 88 weeks at the 25% probability level. The influence of treatment arm on survival was even more significant in the multivariate analysis adjusting for age and KPS ($p = 0.008$; hazard ratio = 0.51). Salvage therapies were well balanced between the

two arms and are not felt to have been a factor explaining this survival difference.

For HT to have potential benefit, an adequate thermal dose must be delivered. Thermal dose-response relationships have been evaluated retrospectively for superficial tumors to allow estimation of thermal dose goals for localized hyperthermia. It has been estimated that a median thermal dose of at least 10 CEM 43°T_{90} needs to be attained to make a meaningful Phase III trial possible (14). The median CEM 43°T_{90} in this trial was 14.1. No thermal dose-response relationship was found; however, this is not surprising as the number of patients evaluated was small, temperature data were limited, and the trial was not designed to look for a thermal dose-response relationship. We feel that brain hyperthermia benefits from the precise catheter placement, made possible by neurosurgical stereotactical technique with image-based treatment planning, and from the lack of pain sensation in the brain. The lack of pain sensation also means that heating must be done cautiously. Acute toxicity with seizures or reversible neurological changes is fairly common, as shown in Table 6. Although these toxicities were generally mild and fully reversible, there is a potential for serious neurotoxicity if heating is not carefully controlled, especially in eloquent cortex or important white-matter tracts. Brain hyperthermia should only be done at a center with the required expertise (7). The reoperation rates for tumor and/or necrosis were slightly higher in the "heat" arm compared with the "no heat" arm (69% vs. 58%). In a previously reported series from this institution, the reoperation rate was 54% for glioblastoma patients who underwent brachytherapy boost without HT (27).

The median survival time reported by Scharfen *et al.* for patients treated with brachytherapy boost for glioblastoma at UCSF before mid1990 was 88 weeks (21). The survival time for the control arm in the current study was slightly shorter, which may be a reflection of differences in patient characteristics. Another possible explanation relates to the fact that 1 year of adjuvant PCV (procarbazine, CCNU, and vincristine) chemotherapy was routinely given after brachytherapy boost through mid1990, but was omitted from the current trial. A separate analysis of this issue is underway.

Efforts need to be applied to better understand how HT benefits patients and to, perhaps, find an easier, more reproducible, and preferably noninvasive means of accomplishing the same end. In the absence of these answers, we are proceeding with another brain brachytherapy/HT trial in which we try to improve thermal dose by heating tumors for up to 90 min per session for up to three sessions. This will be given immediately before brachytherapy and in the middle of brachytherapy (at 72 h) with an optional third treatment immediately after brachytherapy, if necessary, with an objective of attaining a CEM 43°T_{90} thermal dose of 20–50 min.

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