Outpatient Interstitial Thermoradiotherapy

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BACKGROUND. Hyperthermia enhances the cytocidal effect of ionizing radiation. Several pilot studies demonstrated that the combination of interstitial hyperthermia and interstitial radiotherapy (interstitial thermoradiotherapy) is safe and effective. However, these studies mainly utilized low dose rate brachytherapy, and therefore, required hospitalization. With the availability of median or high dose rate brachytherapy devices, we piloted a study to evaluate the feasibility, toxicity and efficacy of interstitial thermoradiotherapy performed in an outpatient setting.
METHODS. Between 1989 and 1993, 27 patients with a diagnosis of carcinoma of the head and neck region (n = 23), carcinoma of the breast (n = 3), or malignant melanoma (n = 1) received 1 or 2 sessions of interstitial thermoradiotherapy. Median patient age was 66 years (range: 37–83 years). Treatment consisted of 60 minutes of 915 MHz microwave interstitial hyperthermia, followed by iridium-192 seed implants, either by Micro-Selectron HDR (10–12 Gray [Gy] in 8.5–21 minutes) or high activity (5–8 mCi per seed) seeds (10–15 Gy in 2–4 hours). In addition to interstitial temperature measurements, a real-time thermal camera was used to monitor the surface temperature spatial distribution. Power supply and/or position of interstitial microwave applicators was adjusted when appropriate. All but one patient also received external beam irradiation prior to implants.
RESULTS. Patients tolerated treatments well although 16 (59%) of them required analgesics during hyperthermia sessions. Skin blisters or ulcerations occurred in only 6 (22%), and all but 2 healed. Complete response occurred in 24 patients (89%), partial in 3 (11%). With a median follow up of 16 months (range: 3–43 months), the 2-year actuarial local control rate was 74%.
CONCLUSIONS. The results of this study indicate that outpatient interstitial thermoradiotherapy is convenient, safe, and efficacious for treating human neoplasms. *Cancer* 1996; 77:2363–70. © *1996 American Cancer Society.*

KEYWORDS: hyperthermia, interstitial thermoradiotherapy, microwave hyperthermia, brachytherapy.

Control for locally advanced or recurrent neoplasms is still a problem in clinical oncology. The efficacy of external beam irradiation is often limited by normal tissue tolerance. Hyperthermia, a relatively new modality of cancer treatment, complements radiation because heat is cytotoxic to radioresistant hypoxic and S-phase cells as demonstrated by in vitro and in vivo experiments.[1–4] Recently, several pilot studies demonstrated the safety and the efficacy of interstitial hyperthermia in combination with interstitial radiotherapy (interstitial thermoradiotherapy) with various types of technology.[5–11] In addition, a study by Arcangeli et al. showed that radiotherapy plus hyperthermia achieved a superior complete response (CR) rate, 85%, compared with a CR rate of 46% for radiotherapy alone for patients with N_2 and N_3 disease of the neck.[12] The technique of iridium-192 afterloading interstitial radiotherapy can be conveniently adapted for microwave interstitial hyperthermia by inserting the antennae (or applicators) into the implanted catheters.[7–18] With the availability of high activity iridium-192 seeds or high dose rate remote afterloading

machine, this treatment can be administered in an outpatient setting without hospitalization. This paper reports the results of a pilot study in evaluating the feasibility, toxicity, and efficacy of outpatient interstitial thermoradiotherapy.

MATERIALS AND METHODS

Patient Population

Between 1989 and 1993, 27 patients including 23 with carcinoma of the head and neck region, 3 with carcinoma of the breast, and 1 with malignant melanoma received a course of interstitial thermoradiotherapy. Eligible patients had local tumors that received radiotherapy as definitive therapy and that were accessible for implants. They also had a life expectancy of more than 6 months and no distant metastasis. There were 10 female and 17 male patients included, with a median age of 64 years (range: 37–83 years). Among 23 patients who had carcinoma of the head and neck region, 22 had metastatic neck nodes for which they received interstitial thermoradiotherapy. One patient had recurrent carcinoma in the nasolabial fold for which he received implants. The primary sites of their disease included: 6 unknown origin; 5 oropharynx; 4 supraglottic larynx; 3 nasopharynx; 3 oral cavity; 1 parotid; and 1 nose. Four of 23 patients with head and neck carcinoma had previously received a course of external beam radiotherapy [dose: 50–60 gray (Gy)]. All 3 patients with a diagnosis of recurrent breast carcinoma had received prior radiotherapy (50–66.6 Gy). The remaining 20 patients received no prior radiotherapy.

In terms of the size of the lesions that received interstitial thermoradiotherapy, 1 patient had a lesion with a greatest dimension of 2 cm; 10, 3 cm; 11, 4 cm; 2, 5 cm; and 3, 6 cm or larger.

External Beam Radiotherapy

Patients who had no prior radiotherapy (20) received a course of conventional external beam radiotherapy with a median dose of 60 Gy (range: 45–70 Gy; fraction size: 1.8 or 2) to the volume of interest utilizing 4 megavolt photons. Six of the 7 patients with prior radiotherapy received a median dose of 50 Gy (range: 10–60 Gy) external beam radiotherapy. Patients were scheduled to receive interstitial thermoradiotherapy 2 weeks following the completion of external beam radiotherapy.

Interstitial Thermoradiotherapy

Patients arrived at our outpatient clinic in the morning, and received premedication 30 minutes prior to their implants. For 24 patients, premedication consisted of intramuscular (i.m.) injections of 5 mg valium, 0.4 mg of atropine, and 75 mg demerol ordered by the radiation oncologist. For 3 patients, premedication was administered by a staff anesthesiologist using intravenous (i.v.) slow drips of fentanyl, midazolam, and morphine sulfate. Tumor volume was outlined on the skin. Needle entrance point, exit point, and path were also marked on the skin. The implantation area was prepped and draped prior to subcutaneous (s.c.) injection of 1% lidocaine into the skin penetration points. Stainless steel needles were inserted in parallel at 1 cm intervals for a single-planar implant, and nylon catheters were pulled through the needles into the treatment volume. In the posterior direction, catheters extended 5 cm beyond the skin exit point. Catheters protruding outside of the skin were close-ended. Two layers of cloth medical adhesive tape were applied to both sides of the exposed catheters to mark the entrance and exit points and to prevent dislodgement of the catheters. The entire procedure was performed in an outpatient setting and usually took less than 1 hour.

The patient was then taken to the simulation room where dummy seeds were placed into each catheter. Radio-opaque wires were placed on the skin to mark the entrance and exit lines. A set of orthogonal films were taken, and the tumor volume was marked on the film. For 23 patients, high activity iridium-192 seeds were utilized (6–8 millicurie per seed, 2 seeds per cm in nylon ribbons) (Best Medical International, Springfield, VA). Dose calculations were performed by software developed in-house and implemented on a minicomputer (VAX 730, Digital Equipment, Maynard, MA). For high dose rate (HDR) implants (4 patients), a Micro-Selectron HDR machine with its accompanying treatment planning system was utilized (Nucleatron Inc., Columbia, MD). The dose for the interstitial radiotherapy (prescribed to 1 cm from central plane of the implant) was 10 to 15 Gy in 2 to 4 hours for a high activity seed implant, and 10 to 12 Gy in 8.5 to 21 minutes for an HDR implant. Twenty-three patients who had received a course of external beam radiotherapy with a dose of 45 Gy or more received only 1 session of thermoradiotherapy. Four patients with an external beam radiotherapy dose of 15 Gy or less received 2 identical sessions of thermoradiotherapy, utilizing the same catheters with an interval of 3 days. In terms of implantation sites, 23 were in the neck, 2 in the chest wall, 1 in the axilla, and 1 in the nasolabial fold.

Following the simulation procedure, and during the dose calculation, patients were taken to the hyperthermia room. Microwave interstitial applicators and temperature sensors were placed into the catheters. For example, a 5-catheter implant required that the applicators be placed into catheters 1, 3, and 5 and the temperature sensors be placed into catheters 2 and 4. For a 6-catheter implant, catheters 1, 3, 4, and 6 were loaded with applicators and catheters 2 and 5 were loaded with temperature sensors. Figure 2 shows a photograph of the catheter arrangement for a patient receiving implants for a metastatic squamous carcinoma in the left neck, as viewed from the angle of the thermal camera. In general, applicators were placed into the first and last catheters. The remaining

catheters were alternated between receiving temperature sensors or applicators. The distance between adjacent applicators was 1 or 2 cm. Care was taken for placing applicators and temperature sensors properly. The junction point (area where microwaves emit from a microwave applicator), as well as the tip of the temperature sensor, was placed at the middle of the tumor volume. The heating pattern of a conventional microwave interstitial applicator, measured in vitro and in vivo, was previously reported by Lee et al.[13] Briefly, the effective heating length of an interstitial applicator is about 5 cm, measured under in vivo conditions. Another temperature sensor was placed on the skin surface at the center of the implant. A microwave (915 megahertz) hyperthermia system (BSD Medical Corp., Salt Lake City, UT) was used for delivering hyperthermia. In addition to interstitial temperature measurements, a real time thermal camera (Hughes Aircraft Company, Carlsbad, CA) was employed to monitor the surface temperature distribution.

Each hyperthermia session aimed to achieve an ideal temperature of 43 °C in the tumor, measured by temperature sensors in the catheters, for a duration of 60 minutes. Power output was regulated by manual control to allow more flexibility in reducing inhomogeneity of temperature distribution and to accommodate patients' discomfort. At the start of a hyperthermia session, the power was set at 3 to 5 watts per applicator and then gradually increased to 10 to 15 watts until the temperature registered by the temperature probes reached 43 °C. The power was then adjusted to maintain a steady state. If a patient could not tolerate 43 °C, we would try the next tolerable temperature by slowly reducing the power output. The treatment goal was to maintain a temperature above 42 °C for 60 minutes. After the completion of hyperthermia, patients were taken to a brachytherapy room for interstitial radiotherapy. The interval between hyperthermia and brachytherapy was 30 to 60 minutes. Following the completion of thermoradiotherapy, the catheters were removed, hemostasis was achieved and the skin in the implanted area was cleansed with alcohol and dressed with bacitracin ointment and sterile gauze. Patients were discharged from the clinic 30 to 60 minutes following the completion of therapy.

Thermal Dose Calculation

Thermal dose was automatically calculated by software of the BSD machine (BSD Medical Corp., Salt Lake City, UT), according to the method published by Sapareto and Dewey.[19] Thermal doses were calculated for all readings from temperature sensors placed stationary inside the tumor (in the interstitial catheters). They were displayed on the screen and printed on a hard copy of the treatment record for each treatment session. It should be noted that in our instrumentation, only one measurement point was contained in a temperature sensor (at the tip) and, therefore, only one temperature reading was obtained in a catheter.

Thermal Camera Imaging

A Probeye Thermal Video System (Hughes Aircraft Company, Carlsbad, CA) continuously monitored the temperature distribution over the entire surface during hyperthermia treatments. The camera collects infrared radiation (wavelength 2–6 microns) emitted from the surface. The radiation passes through infrared transparent windows (silicon), reflects from a continuously rotating wedged mirror (1 of 10 mirrors), and is detected by 1 member of a vertical stack of 10 argon gas cooled InSb detectors. The camera can resolve 2 objects (having different temperatures) separated by 2 mm for objects located 1 M away. Detected radiation is converted to a temperature on the skin surface and is not a measure of deep seated tissue which is measured with temperature probes placed in the interstitial catheters. To aid in the discrimination of small temperature differences, the two-dimensional temperature distribution was color encoded by the processor. The camera provides a 16-level gray scale or a 16-color thermographic image. The appropriate detected temperature distribution (usually 30–43 °C) can be selected that enhances image contrast, temperature sensitivity, and resolution. The latter is determined by the total temperature range divided by the number of gray scale, or 16 in this case. Therefore, the temperature resolution of the images obtained by the thermal camera is 13 of 16 or 0.8 °C. To provide a secondary check of the thermal camera, a thermometer probe was placed on the patient's skin at the center of the treatment volume with a piece of black electric tape (emissivity: 0.98, same as human skin). Nevertheless, the surface thermometer read slightly lower (about 0.8 °C) than regions close to it as monitored with the thermal camera due to poor thermal contact with the skin through the thin tape. To ensure accurate thermography, the camera window was mounted parallel to the central treated surface area. In regions of high skin curvature, incorrect temperature readings could be as large as 1.5 °C. During treatment, patient movement occasionally required repositioning of the camera to ensure more accurate thermometry. As part of the patient's records, thermographic images of the patient's surface temperature during the hyperthermia treatment session were recorded on VCR tapes.

RESULTS

Treatment Related Toxicities

All patients received a course of thermoradiotherapy. Pain or discomfort was experienced by 16 patients (59%) who required analgesics during the hyperthermia session. Skin blistering or ulceration occurred in 6 patients (22%),

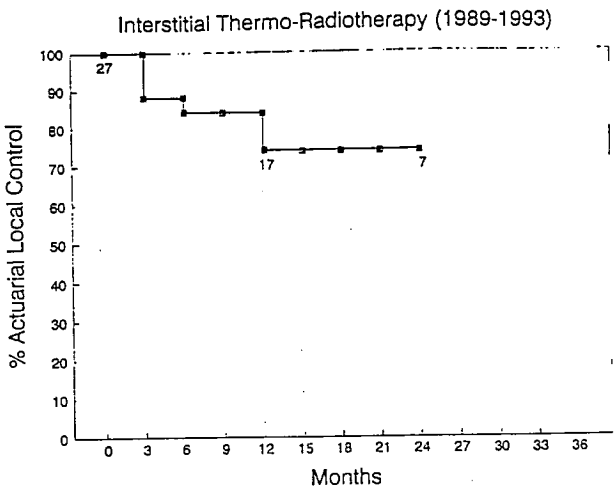

FIGURE 1. Actuarial local control for 27 patients following interstitial thermoradiotherapy.

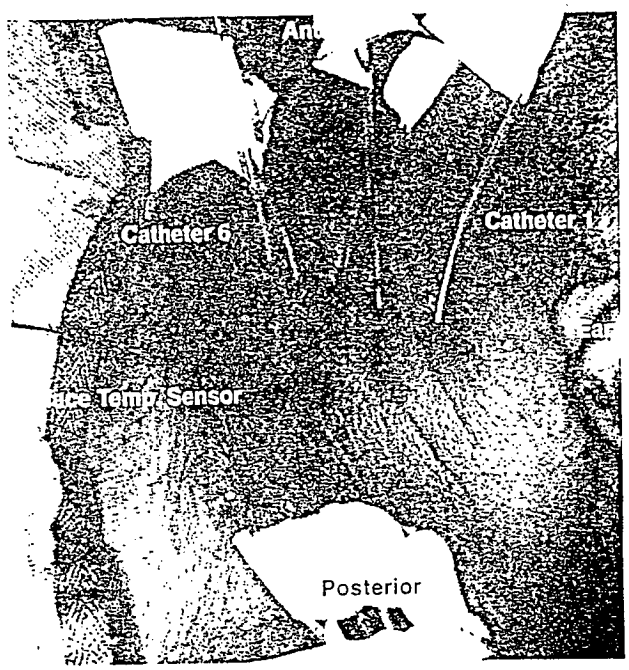

FIGURE 2. The still photograph of a patient (in supine position) who had 6 catheters inserted in the left neck. Catheters 1, 3, 4 and 6 were loaded with microwave interstitial applicators, and catheters 2 and 5 were loaded with temperature sensors. Another temperature sensor was placed on the skin at the center of the implant.

and all but 2 healed. These 2 patients had prior external beam radiotherapy for breast cancer. The local complication rate was 2 of 12, or 17%, for 12 patients who had a tumor size of 2 to 3 cm versus 4 of 15, or 26%, for 15 patients who had a tumor size of ≥4 cm ($P = 0.44$).

Local Control

CR was achieved in 24 patients (89%), and partial response (PR) in 3 patients (11%). Three patients with an initial CR developed recurrence in the implanted area, 7, 9, and 15 months following therapy. No marginal recurrence was seen. Thus, a total of 6 patients (3 persistent and 3 recurrent) failed in the implanted area, with a median follow-up of 16 months and a range of 3 to 43 months. The 2-year actuarial local control rate for all patients was 74% (Fig. 1). In 20 patients who had no previous radiotherapy, local control was achieved for 18 (90%). The incidence of local failure in 11 previously untreated patients who had received a total dose of 6400 to 7200 cGy (external beam + brachytherapy) was 1 of 11, or 9%, versus 1 of 9, or 11%, for 9 previously untreated patients who had received a total of 7200 to 8200 cGy ($P = 0.71$). For 7 patients who had previous radiotherapy, local control was achieved for 3 (43%). The difference of the local control rates between these two groups was statistically significant with a P value of 0.023 (Fisher's exact test). Age (37–66 versus 67–83 years), sex (male *versus* female), histology (squamous *versus* all others), and implantation site (neck *versus* all others) did not affect treatment outcome.

Thermal Dose, Local Complication, and Local Control

Thermal doses were calculated as equivalent minutes at 43 °C or at 42.5 °C. The results showed that the value varied among patients. The median dose was 24.1 equivalent minutes at 43 °C (range: 1–83 minutes) or 41.3 equivalent minutes at 42.5 °C (range: 1–119.5 minutes). For the purpose of analysis, patients were divided into 3 groups based on the calculated maximum thermal dose at 42.5 °C: Group A, ≤60 minutes, 9 patients; Group B, >60 but ≤30 minutes, 9 patients; and Group C, >30 minutes, 9 patients. The local complication rate was 1 of 9, 4 of 9, and 1 of 9 for Groups A, B, and C, respectively. The difference in complication rates among these three groups was not statistically significant ($P = 0.14$). Using local control as the end-point, the local control rate was 6 of 9, 7 of 9, and 8 of 9 for Groups A, B, and C, respectively, ($P = 0.52$). This noncorrelation between thermal doses and biologic end-points (complication and local control rates) was also seen when analyses were repeated by using average or minimum calculated thermal doses.

Patient Survival

At the time of this analysis, 9 of 27 patients were alive with no evidence of disease. Median follow-up was 33 months with a range of 14 to 43 months. Of the 21 patients who achieved local control, 5 died of distant metastases, 5 of recurrent disease at the primary site in the head and neck region, and 2 of intercurrent disease. The 2-year actuarial survival rate for the entire group was 40%.

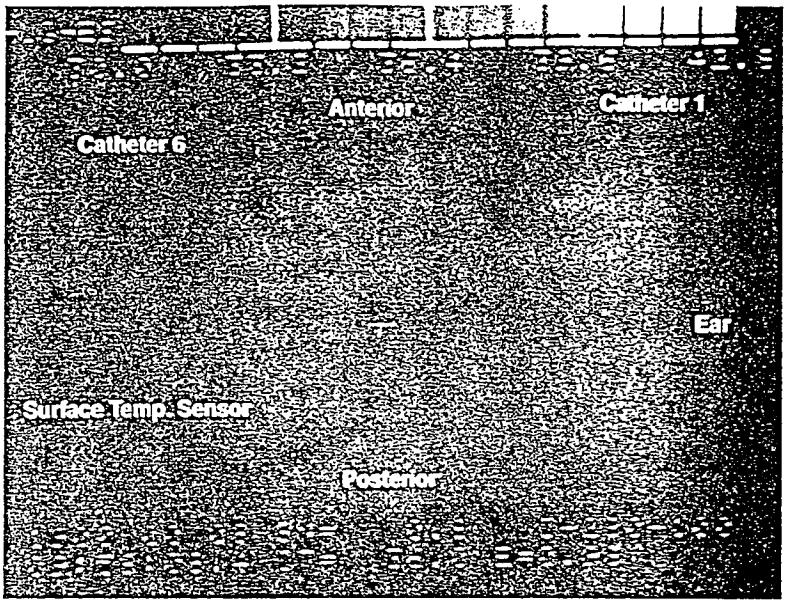

FIGURE 3. A thermal camera image of left neck of the same patient at beginning of the interstitial microwave hyperthermia session. The location of the temperature sensor at the skin surface was changed slightly from Figure 2 because of dislodgement and re-attachment.

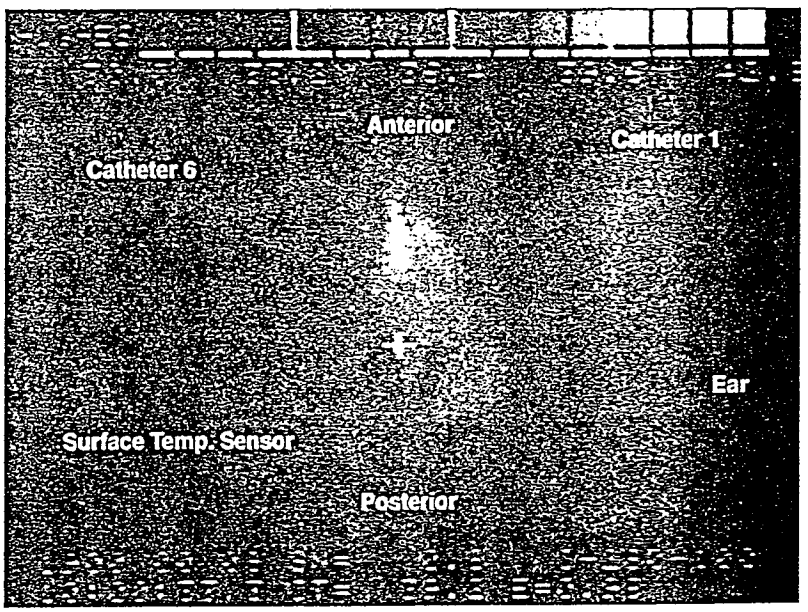

FIGURE 4. Same as Figure 3 the timing was 2 minutes into the hyperthermia session.

Temperature Distribution Obtained by Thermal Camera

The temperature spatial distribution on the surface of the implanted area was captured by the thermal camera. The thermal images were obtained just prior to and during the hyperthermia session. In the beginning of the hyperthermia session, thermal images showed inhomogeneous thermal distribution with hot spots around the applicators (Figs. 3 and 4). This finding is consistent with the specific absorption rate (SAR) patterns of the microwave interstitial applicator that we have measured under in vitro conditions.[4] Six minutes into the treatment session, the thermal images showed a more homogeneous temperature distribution pattern (Fig. 5), probably due to thermal conduction, convection, and vascular perfusion. Based on thermal camera images taken at the initial phase of the hyperthermia session, 2 patients had an ad-

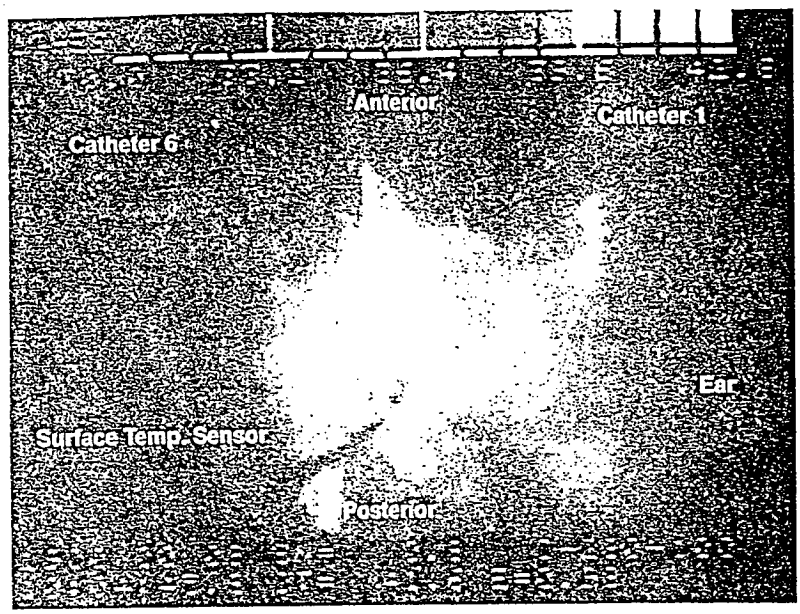

FIGURE 5. Same as Figure 4, the timing was 6 minutes into the hyperthermia session.

justment of applicator position (more than 1 cm) to achieve a more homogenous and more centrally located heating pattern.

DISCUSSION

The biologic basis of using heat in treating human neoplasms has been extensively studied and reviewed.[1-4,20] Hyperthermia produces cell killing in radioresistant hypoxic and S-phase cells and potentiates cytocidal effects of ionizing radiation. This complementary feature of hyperthermia with radiation has created great enthusiasm in combining the two treatment modalities. Interstitial hyperthermia, similar to interstitial radiotherapy, has the advantage of treating tumor volume while sparing surrounding normal tissue. As early as 1971, Sutton explored the use of interstitial hyperthermia induced by a resistor heating device for treating malignant gliomas.[21] However, technology for interstitial microwave hyperthermia was not available for clinical use until Taylor and Strohbehn et al. developed micro dipole applicators in the late 1970s.[22,23] Relative to other techniques, such as resistor heating, circulating hot water, and radiofrequency, microwave interstitial hyperthermia has the advantage of producing a more homogeneous heating pattern.[24] Our thermal camera pictures obtained during the treatment session demonstrated a rather homogeneous spatial temperature distribution, although it reflected only the surface temperature. The use of a thermal camera also enabled us to adjust the power or applicator position when a suboptimal heating pattern was detected.

Interstitial thermoradiotherapy in this study was administered in an outpatient setting, and no hospitalization was required. The treatment was convenient and well tolerated. This was supported by the fact that 23 of 27 patients required only i.m. premedication.

In this series, treatment induced toxicities were mild and manageable. Although 6 patients (22%) developed blisters or ulcerations, all but 2 healed with conservative management. Among these 2 patients, 1 who previously received a course of radiotherapy (50 Gy), developed a persistent 1.5 cm skin ulceration on the chest wall. This patient was without evidence of disease 19 months following interstitial thermoradiotherapy. Another patient who previously received 66 Gy had persistent tumor on the chest wall that progressed and became ulcerative. Our experience of toxicities associated with interstitial thermoradiotherapy was similar to those reported in the literature.[15-17] Petrovich et al. reported a 20% incidence of blistering or moist desquamation and a 5% incidence of skin necrosis.[15] Emami et al. treated 46 patients with a diagnosis of recurrent or persistent tumors with interstitial thermoradiotherapy, and observed a 12 of 46 (26%) incidence of moderate to severe complications which included delayed wound healing, delayed necrotic crater, cutaneous, orocutaneous fistula, and vesicovaginal fistula.[16] Seegenschmiedt et al. reported that 19% of 62 patients treated by thermoradiotherapy for head and neck tumors had Grade 1 or 2 acute toxicities, 11% had long term side effects, and 3% required surgical intervention.[17] Interestingly, these complication rates for interstitial thermoradiotherapy are not higher than the reported complication rates for interstitial radiotherapy.[25,26] It appears that the addition of interstitial hyperthermia to interstitial radiotherapy does not increase this type of toxicity.

Similar to our experience, many investigators reported excellent initial response rates with interstitial thermoradiotherapy.[5,6,8-11,15-18] A summary of published results of treating head and neck cancer with interstitial thermoradiotherapy was included in a paper by Seegenschmiedt et al.[17] Briefly, the literature showed a 56% CR and a 28% PR rate.[17] Unfortunately, only a few investigators reported long term results. Seegenschmiedt et al. reported a 1-year local control rate of 58% and a 2-year survival rate of 52%.[17] Petrovich et al. reported a 64% CR rate and a 22% 2-year survival for 39 patients with recurrent tumors of various sites.[15] Emami et al. reported that local control was achieved in 23 of 46 patients (50%), 6 to 48 months following therapy.[16] Engin et al. reported a 67% local control rate for 9 patients with advanced head and neck cancer with a mean follow-up of 21 months.[18] The efficacy of thermoradiotherapy is also demonstrated by our 74% 2-year actuarial local control rate. These trials, including ours, should be viewed as pilot studies. They provide a base for conducting future randomized clinical trials in answering the question of whether or not interstitial hyperthermia improves local control rates by radiotherapy alone, and what type of tumors will benefit from adding interstitial hyperthermia to radiotherapy.

A limited number of interstitial temperature probes reduced the validity of our thermal dose analyses. Our instrumentation only allowed us to measure temperature at one point in a catheter at a time. By no means did our thermal dose calculations reflect a total picture of thermal distribution at depth. Although the thermal camera demonstrates a rather homogeneous surface temperature distribution, it is conceivable that a few cold spots near blood vessels at depth were not detected by interstitial temperature probes. Surface temperatures measured by the thermal camera correlated with the temperature measured by temperature probes placed in the catheters. This is because the implants were generally no more than 3 cm deep. In our experience, tumor temperatures at depth were usually no more than 2 °C higher than surface temperatures. A thermometry subsystem with an array of sensors in each catheter is more desirable in this regard. Nonetheless, adding more sensors probably would not enable us to deliver a higher thermal dose because we believe that our patients had received maximum tolerable hyperthermia treatment in a given session. In our experience, temperature mapping has enabled us to better regulate the power distribution for better uniformity. Changes in blood flow during hyperthermia can perturb the temperature distribution. The power to the applicators should be appropriately adjusted. A patient's pain threshold also limits the ability to heat. Using a thermal camera to guide the operator, other applicators can be adjusted to minimize temperature gradients over the region of interest and compensate for heat loss due to fluctuation of blood flow.

Most of the reports of interstitial thermoradiotherapy used low dose rate iridium-192 seeds and required hospitalization. With the advent of high activity iridium seeds and high dose rate remote loading brachytherapy machines, interstitial radiotherapy can be accomplished within minutes or hours. Therefore, interstitial thermoradiotherapy can be administered on an outpatient basis. Our pilot study demonstrated that outpatient interstitial hyperthermia was convenient, safe, and efficacious in treating human neoplasms.

During the 4-year period of this pilot study, our treatment philosophy was slowly evolving and, therefore, there were some variations in treatment prescriptions. Having accumulated the experience in this pilot study, we now routinely prescribe 10 Gy for interstitial brachytherapy and 60 minutes at 43 °C for interstitial hyperthermia in addition to external beam radiotherapy.

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