Anatomical Site-specific Modalities for Hyperthermia

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Abstract

The clinical application of hyperthermia in the treatment of deep-seated tumors remains an empirical science. The pleomorphic nature of the neoplasms and the great diversity in the anatomy and physiology of the individual tumor locations make the treatment of nearly every neoplasm a unique challenge.

A wide variety of devices is required, both for the administration of hyperthermia and for the measurement of the temperatures achieved. At Stanford University, these include the BSD Medical Corp. annular phased array system, an isospherical ultrasound device, and interstitial radiofrequency for deep heating. Ultrasound transducers and a variety of microwave applicators are used for superficial hyperthermia. Six illustrative case studies, selected from the 91 patients treated in our program since October 1981, are presented, with discussion and comparison of treatment devices. Difficulties in deep heating were encountered in several instances, believed secondary to the thickness of the s.c. fat, the relatively high heat-induced tumor blood flow, and the presence of adjacent bone. It is suggested that ultimate improvement in clinical results will be possible once a better understanding is achieved of such anatomical and physiological factors.

Introduction

Clinical studies of ultrasound-induced local hyperthermia for the treatment of superficial cancers were introduced at Stanford in the late 1970s by Marmor et al. (4, 5). Superficial neoplasms of a variety of histologies, usually cutaneous metastases, were treated with either 2.0- or 4.0-cm-diameter piezoelectric transducers at frequencies of 1 to 3 MHz. Some of the hyperthermia treatments were also combined with radiation. These studies demonstrated that complete and partial regressions could be obtained in some neoplasms with hyperthermia alone (4, 5) and that the response rates could be improved by combinations of hyperthermia and X-irradiation (2, 3).

These investigations were sufficiently encouraging to establish a clinical hyperthermia program for continued studies. A hyperthermia suite was constructed which consists of a treatment room isolated by appropriate MW shielding and adjacent facilities for power supplies and monitoring equipment for a variety of MW and ultrasound devices for the production of local and regional heating. A second series of patients was treated beginning in October 1981, and since then, 91 additional patients have been studied. Both superficial and deep neoplasms have been treated, and a variety of applicators have been evaluated. This experience has demonstrated that, because of the pleomorphic nature of the neoplasms, the diverse anatomy and physiology of the individual tumor sites, and the difficulty in determining temperature distributions, nearly each treatment is unique. Therefore, a wide variety of devices, both for the application of the heat and the measurement of the achieved temperature, is required. Thus, it is not possible within this clinical experience at this time to present systematic data on efficacy and outcome. On the other hand, it is possible to learn some of the technical aspects of operating these various devices, to learn some of their limitations, and to compare one device against another in various anatomical sites. Therefore, 6 case studies were selected from the 35 patients who have been treated during the past year which demonstrate the variety of problems encountered, the solutions to these problems, and an intercomparison of the heating methods.

Materials and Methods

For the case studies described below, the following devices for inducing heating have been evaluated: (a) the isospherical ultrasound device, a device for deep heating with ultrasound energy; (b) ultrasound transducers for superficial heating; (c) MW transducers for superficial heating; and (d) the BSD Medical Corp. APAS for regional deep heating.

Ultrasound. Most of Stanford's ultrasound equipment has been designed and fabricated in-house. One exception is the deep-heating isospherical ultrasound device, which was the result of a cooperative effort between Stanford and Hewlett-Packard Co. (Palo Alto, CA) (1). This system consists of an array of 6 planar PZT-4 discs (7-cm diameter) mounted on a spherical shell segment such that the array is geometrically focused to produce a high-ultrasound-intensity region at the system isocenter (i.e., the center of curvature for the sphere, 26 cm). Each disc operates within 20 kHz of the fundamental frequency (350 kHz), and the system generates a total acoustical power of 200 watts. The system is being evaluated clinically for heating tumors with diameters of 3 to 8 cm located, generally in the pelvic region, at depths up to 12 cm.

The superficial ultrasound heating transducers are also planar, of various diameters (i.e., 2, 4, 6, and 8 cm), and operate at 1 to 3 MHz. Thus far, the most successful clinical transducer has been the 8-cm-diameter PZT-4 disc operating at 2 MHz with a maximum acoustical power of 45 watts.

MW. MW hardware is a combination of the BSD Model 1000 system (BSD Medical Corp., Salt Lake City, UT) and several prototype devices designed and fabricated by Varian Associates (Palo Alto, CA). For deep heating, we are evaluating the BSD APAS (7). This system operates over the range of 60 to 100 MHz with maximum available power of 2000 watts. This device is considered most suitable for regional applications in the lower abdomen and pelvis.

Superficial MW heating devices include the waveguide and horn applicators, which are part of the BSD system, and a set of microstrip (spiral) antennas designed by Varian (6). Two power supplies are used for superficial treatments. The BSD supply covers the frequency range of 50 to 1000 MHz with maximum power of 150 watts. The other power

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: MW, microwave; CT, computerized tomography; APAS, annular phased array system.
source was provided by Varian Associates and operates from 400 to 460 MHz with maximum net power of 200 watts. The small microstrip spiral antenna applicators (Fig. 1) are generally as effective as the waveguide devices, and for clinical treatments, they have a considerable advantage because of their small size. For example, they are compatible with the concavities and convexities of the head and neck region. The BSD single horn applicator (Fig. 2) (driven at 300 or 433 MHz) remains our choice for larger treatment fields, e.g., chest wall. However, the size of heat fields produced by our present equipment remains limited.

Thermometry. Thermocouples are used to measure temperatures for ultrasound treatments. High-resistance thermistor probes (BSD Model 1000 system) are used for MW. Good thermometry is essential in this learning and development stage of hyperthermia and, therefore, it is necessary to be aggressive in temperature measurements, inserting as many interstitial probes as practical. Pull back temperature mapping is used with the MW thermometry system routinely. This involves moving a probe within an interstitially inserted catheter in order to measure temperature along a linear track. Until recently, it was not possible to map temperature fields in ultrasound treatments, because of artifacts associated with plastic catheters used for the pull-back technique. Multisensor thermocouple probes (18 gauge), which have up to 10 sensing elements, have been developed and can be used effectively with minimum artifact in the ultrasound treatment.

This has greatly expanded temperature data acquisition and will allow better comparison of the temperatures achieved with the 2 modalities (MW, ultrasound).

Case Studies

Case 1. The patient is a 74-year-old female with carcinoma of the breast since 1953. She remained free of recurrent disease until 1968, when she developed a right parasternal mass. Between 1968 and 1981, she received several courses of orthovoltage radiation to the chest wall to maximum radiation tolerance (over 6000 R). When initially seen at Stanford, a 5- x 6-cm exophytic lesion was present over the left parasternal region with the surrounding skin showing marked chronic radiation epidermitis. Between February 14, 1984, and March 2, 1984, the patient received 1980 rads in 11 orthovoltage treatments over 17 days at 180 rads/day. During the same time, she received 6 hyperthermia treatments at approximately 3-day intervals. Part of the first was given with a single-horn BSD MW applicator at 424 MHz. The remainder of the first treatment and all of the next 5 were given with the Varian spiral applicator. The patient had an appreciable reduction in the size of the mass by the termination of treatment, and at 2 weeks follow-up, continued regression was noted (Fig. 3). Thermal distributions are illustrated in Chart 1. The treatment site was equally accessible for both devices. The horn applicator encompassed more normal tissue, and consequently, the attempt to heat with this device was pain limited. Therefore, in this case, a considerable advantage is noted for the spiral applicator, which was able to achieve temperatures as high as 47°C with a reasonably homogeneous temperature profile.

Case 2. The patient was a 58-year-old white female with a T2N1 squamous cell carcinoma of the floor of the mouth diagnosed in April 1982. Following preoperative chemotherapy and subsequent incomplete resection, she received 7000 rads to the primary site and 5000 rads to the neck bilaterally. In October 1983, she developed lung metastases and a left posterior cervical mass. This mass grew progressively, although the patient was treated according to several chemotherapeutic protocols.

The problem involved a recurrent, rapidly growing squamous carcinoma in the left neck, which had been irradiated to 5000 rads previously. Examination revealed 2 adjacent masses, 5 x 7 x 4 cm and 3 x 3 x 4 cm. On CT scan, these masses were considerably larger than they appeared by surface measurement. The treatment included irradiation at 200 rads/day, 10 treatments in 16 days at 6 MV, to a total dose of 2000 rads. The larger mass was treated with heat 5 times with various heating applicators: a single-horn MW applicator at 422 MHz; a 6-cm ultrasound transducer at 2 MHz; and the 8-cm-diameter spiral applicator at 433 MHz. The smaller lesion was also treated with hyperthermia on 5 occasions, once with ultrasound and 4 times with the spiral applicator.

The gross tumor before and after therapy is illustrated by the CT scan (Fig. 4). Note the substantial reduction in mass. Temperature profiles at 1- and 2.5-cm depths are illustrated for each of the 3 applicators (Chart 2, A and B). The temperature profiles obtained with the MW devices are typical, showing high central tumor heating with a substantially cooler periphery. At 2.5 cm depth, there is an advantage with the horn, probably due to the larger radiating aperture. Ultrasound devices generally show broader, more uniform temperature distribution and, in this com-

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parative study, gave a substantially better treatment at depth (2.5 cm). The patient had a significant reduction in mass for each of the 2 lesions. She had slight blistering attributed to the ultrasound applicator, but she had no discomfort within these lesions. The epithelial surface of the larger tumor, which was essentially denuded at the beginning of treatment, recovered remarkably so that at her last follow-up, 6 weeks following the initiation of treatment, both lesions were dry and essentially flat, and the surface epithelium was partially reconstructed.

Case 3. The patient is a 51-year-old black male with recurrent Stage B2 adenocarcinoma of the colon (status, post-partial colectomy). In June 1982, following documentation of pelvic recurrence, the patient received radiation to the left abdomen and pelvis: 5040 rads in 28 treatments over 41 days followed by a 1000-rad boost in 5 treatments over 6 days. The patient developed a progressive pelvic mass, and between December 9 and December 29, 1983, 1980 rads in 11 treatments over 20 days were given. Concurrently, the patient received 5 APAS treatments at 3-day intervals to the pelvis in an attempt to treat the well-defined mass in the left pelvic region.

During the application of MW energy, the temperature rapidly increased in the area of the tumor that was presumed necrotic or cystic (Fig. 5). Substantial heating occurred within the central
tumor, with temperatures recorded in excess of 47°C (Chart 3). These temperatures could be easily maintained at relatively low-power levels (600 to 700 watts), indicative of a very low perfusion rate. Tumor external to the necrotic or cystic core and adjacent to normal tissue remained substantially cooler (39 to 40°C) throughout the treatment.

The temperature catheters were left in place, and antibiotic ointment was applied surrounding the points of exit. There were no cutaneous changes. Approximately 2 weeks following this therapy, the patient was hospitalized with an abdominal wound dehiscence. On January 25, 1984, an extended incision was made into the left lower quadrant. The cystic mass noted on CT was drained, biopsies were taken, and necrotic material was removed. The biopsies revealed persistent adenocarcinoma. The patient has been supported by frequent debridement and drainage of his abdominal wound. In spite of achieving therapeutic temperatures (47°C) throughout most of the tumor, as of March 8, 1984, the patient continued to have abdominal wound infection, dehiscence, and fungating tumor. Upper gastrointestinal series demonstrated a jejuno-cutaneous fistula, and the subsequent course has been febrile.

**Case 4.** The patient is a 39-year-old white female first seen in June 1983, 6 years following an excisional biopsy of a malignant melanoma from the left cervical region. Left radical neck dissection revealed no adenopathy. She was free of disease until a solitary lytic lesion was discovered in the distal right femur in February 1983. CT scans showed cortical destruction and soft tissue tumor surrounding the bone and extending into the medullary canal (Fig. 6). Biopsy confirmed malignant melanoma. The patient received 5900 rads in 19 treatments over 36 days at the rate of 300 rads/day between June 24 and July 28, 1983. During this time, she also received 7 treatments in the APAS given every 3 to 4 days and one treatment with the isospherical ultrasound device. She also received 9 doses, 6.250 g, of the radiosensitizer SR2508. The patient tolerated the series of treatments with considerable pluck. After the fifth treatment, an area of discoloration deep to the skin was noted in both the lateral posterior and medial thigh. This was a s.c. ecchymosis which on palpation was indurated relative to adjacent tissue. It was interpreted as a deep s.c. burn. After 7 unsuccessful attempts to achieve therapeutic heating with the APAS, a final attempt was made with the isospherical ultrasound device, and again it was not possible to achieve therapeutic heating.

Heating occurred only in the adjacent striated muscle and s.c. fat with the APAS. No heating occurred within the neoplasm itself, either exterior to the femur or within the marrow cavity (Chart 4). The isospherical ultrasound device heating was within the tumor region but minimal (Chart 5). Pain during the ultrasound treatment was substantial, presumably due to the excessive absorption in bone.

Because of the fear of a pathological fracture, on September 27, 1983, 2 months following the conclusion of combined therapy, the remaining neoplasm was resected by curettage, and the femur was fixed with Rush rods and methyl methacrylate. Pathology revealed malignant melanoma similar to that seen prior to treatment. There was no apparent decrease in cellular viability.

The patient has subsequently resumed normal activity and normal weight bearing. She has remained well without evidence of further progression for 10 months. Although it is not conclusively evident why it was not possible to achieve therapeutic heating in this situation, 2 factors might be implicated: (a) the neoplasm was partially surrounded by dense cortical bone, which effectively shielded the mass from MW conduction currents; (b) the area of involvement was traversed by popliteal vessels which effectively compensated absorbed MW and ultrasound energy via perfusion washout. With respect to the latter, an analysis of thermal washout rates (*i.e.*, rate of tissue cooling after power is terminated) at multiple sites shows that the rates of heat loss in tumor were as high as those measured in surrounding muscle. Also, during the ultrasound treatment, pressure applied in order to occlude the femoral artery

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Chart 3. Temperature distributions obtained during treatment with the APAS. Temperatures were measured using the pull back technique, moving a Bowman thermistor probe inside a catheter insert. Solid line through the tumor (f), catheter track. Shaded region within the tumor, necrotic or cystic core. b, bone.
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showed an immediate increase in tumor temperatures (Chart 6). It is clear that this neoplasm was at least as well perfused as normal tissue. However, one would expect that treatments with the APAS would have produced similar temperatures in both normal and tumor tissue under such circumstances. This was not the case and gives support to the supposition that surrounding bone shielded the region from conduction currents.

Case 5. The patient is a 57-year-old white male (status, postresection of a Dukes' Stage B2 adenocarcinoma of the rectum which dates from November 1981). A pelvic recurrence was noted in September 1982, and a second anterior-posterior resection of the mass was performed, but gross residual tumor remained in the sacral hollow. In October 1982, 4680 rads were administered through 4 pelvic fields followed by multiagent chemotherapy. The neoplasm recurred in October 1983 with a pelvic mass, which eroded the sacrum and produced urinary symptoms of incontinence, frequency, and nocturia every 45 min. The tumor extended from the superior margin of the sacroiliac joint inferiorly to the perineum.

The patient already had had extensive full pelvic irradiation and multiagent chemotherapy and was severely symptomatic with recurrent presacral adenocarcinoma of the colon. The possibility of further irradiation was severely limited by the previous therapy; the tumor was situated within the sacral hollow, and
attributed this reduction in symptoms to the therapy. This report, The patient returned for follow-up 3.5 months posttherapy and reported a marked reduction in pain and urinary symptoms. He conclusion of therapy, there was little indication of any benefit. deep placement of the pelvic probe catheters. At the time of the attemptments were limited by pain for all heating attempts. difficulties associated with temperature probe placement. Treat tumor. For subsequent treatments with the isospherical ultrasound device (Chart 8), therapeutic temperatures were achieved in the sound device, good heating could not be documented due to hand, for the first treatment with the isospherical ultrasound device directed towards the anterior aspect of the sacrum. The heat treatments were given every 3 to 6 days during the course of his radiotherapy. Chart 7 demonstrates representative temperatures achieved with the APAS. Note that therapeutic temperatures were not achieved throughout the main portion of the mass and that the highest temperature was probably in the s.c. fat. On the other hand, for the first treatment with the isospherical ultrasound device (Chart 8), therapeutic temperatures were achieved in the tumor. For subsequent treatments with the isospherical ultrasound device, good heating could not be documented due to difficulties associated with temperature probe placement. Treatments were limited by pain for all heating attempts. The combined modality treatment was terminated prematurely at the patient’s request because he could no longer tolerate the deep placement of the pelvic probe catheters. At the time of the conclusion of therapy, there was little indication of any benefit. The patient returned for follow-up 3.5 months posttherapy and reported a marked reduction in pain and urinary symptoms. He attributed this reduction in symptoms to the therapy. This report, however, is complicated by the fact that the patient also received 5-fluorouracil, mitomycin C, and hexamethylmelamine in the interim. Nevertheless, the patient was in remarkably good general condition, and it is likely that his sense of well-being and symptomatic relief resulted from the combined therapy. The case is of interest because, while the presacral hollow did not heat well with the APAS, therapeutic temperatures were obtained with the isospherical ultrasound device in that part of the neoplasm not shielded behind the sacrum.

Case 6. A 65-year-old white male received 4800 rads to the entire pelvis and a 2000-rad boost to the prostatic fossa in March 1981 for a poorly differentiated adenocarcinoma of the prostate. The radiation followed a suprapubic prostatectomy. In July 1981, the patient became obstructed. A transurethral resection of the prostate was performed, and at that time a nodule was noted in the right corpus cavernosum. Biopsy revealed adenocarcinoma of the prostate, and he was placed on diethylstilbestrol, 1 mg daily, and megestrol acetate. During the 3 months prior to evaluation for hyperthermia and in spite of the hormone deprivation, the penile lesion extended throughout the entire shaft and erupted through the skin of the glans creating a fungating excrescence approximately 2 cm in diameter. Also, the patient had persistent and gross hematuria and partial urethral obstruction, requiring drainage by a suprapubic cystostomy. The problem was to treat that portion of the neoplasm which had directly extended into the penile corpora, even though this region was immediately adjacent to the prostate and bladder irradiated previously. Provisionally, the patient was to have received 5600 rads to the entire penis and base of bladder. At the same time, he was to be treated with hyperthermia induced by the APAS. Temperature measurement was carried out by a transurethral catheter containing a Bowman thermistor probe. The treatment extended between September 22 and October 19, 1983. Radiation therapy was interrupted after 3056 rads because of moist desquamation. During the rest period, he developed symptoms of spinal cord compression, and this was treated by external-beam irradiation at another institution. The patient failed to return immediately to resume radiation therapy to the penis, although he did return for follow-up sometime later. Remarkably, the patient recovered following the treatment of his spinal cord compression, and when he returned for follow-up examination approximately 3 months following the combined treatment to the penis and base of the bladder, the extensive infiltration of the penis had grossly diminished, and the fungating lesion through the skin of the glans penis had healed completely. It is likely that he received an additional 1000 rads to the penis during the course of the irradiation for the spinal cord compression. The patient’s gross and persistent hematuria had also completely subsided. He was examined again 4.5 months following therapy, at which time he reported that the mass within the penis had continued to shrink and that the hematuria remained under control. Examination disclosed a penile shaft approximately 7 cm long with palpable induration but no knobby neoplasm as noted initially. Also, the area of fungation on the glans remained quiescent.

Comment

The patient was placed in the APAS in position to heat the lower pelvic region. Saline bokus (0.4% NaCl solution) was used
to overlay the groin and penis region to smooth the contour and insulate the area from the cooling and coupling bolus. A frequency (70 MHz) was used to offset the internal electrical fields toward the anterior regions. This shift in electrical field intensity was documented using external electrical field probes. The consequent shift in power density and bolus insulation resulted in superficial heating and, no doubt, contributed to the acute skin reaction which was severe enough to provoke interruption in the treatment schedule. The intraurethral catheter seemed to work well for monitoring the temperature (Chart 9). However, the precise tumor temperature cannot be inferred from these data. It would have been awkward, if not impossible, to place interstitial probes in the corpora cavernosa.

**Discussion**

The reality of present-day hyperthermia treatment rests in the fact that there is great diversity in the anatomy and physiology of the treatment sites. Beyond this, other anatomical and physiological factors, such as the thickness of s.c. fat, the relative blood flow through the neoplastic tissue, and the presence of bone and air cavities, are all factors which limit the effectiveness of tissue heating and therefore the efficacy of the treatments. For the present, it appears that a variety of hyperthermic devices will be required in order to provide optimum individualization of treatment. It is felt that only by an extended program (years) of careful comparative testing of alternative equipment at
each tumor site will sufficient information ultimately be obtained to suggest what approach will be most advantageous for each individual tumor. Additional phantom and animal studies in which selected parameters can be more readily manipulated may aid in expediting this process.

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References

Fig. 1. Spiral microstrip MW applicators used for superficial hyperthermia treatments at 433 MHz (large) and 915 MHz (small). These applicators are used with 1.5-cm water coupling and cooling bolus (right). Composite of applicator and bolus (upper left).

Fig. 2. BSD MW horn applicator used for superficial hyperthermia at frequencies of 310 and 433 MHz. This applicator is used with 3 to 4 cm of water coupling and cooling bolus (not shown).
Fig. 3. CT scan before (right) and after (left) hyperthermia and 1980-rad orthovoltage treatments of 5- x 6- x 3-cm parasternal mass. Six hyperthermia treatments given with spiral microstrip applicator; one attempted treatment with horn applicator.

Fig. 4. CT scans before (left) and after (right) hyperthermia and radiation treatments of squamous carcinoma of neck. Hyperthermia was given with MW and ultrasound modalities. Temperature distributions obtained with 2 MHz ultrasound were considered better than those obtained with the MW devices. See Charts 2, A and B.
Fig. 5. CT scan of left pelvic mass shows distinct change in image density in the central tumor which indicates a necrotic or cystic core.

Fig. 6. CT scan confirmation of malignant melanoma in distal femur.
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