BSD Medical Corp.
BSD-2000 Hyperthermia System
Essential Prescribing Information

Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician trained in the use of this device.

Caution: All operators must thoroughly read and understand all sections of the Operator Manual before performing a procedure using the BSD-2000. Failure to understand and follow instructions may cause injury to the patient and/or user and/or damage to the equipment and could result in improper functioning of the system.

Caution: The BSD-2000 System is to be used only by qualified operators upon the prescription and under the supervision of a physician who is experienced in clinical hyperthermia.

Humanitarian Use Device. Authorized by Federal law for use in the treatment of cervical carcinoma patients who would normally be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors. The effectiveness of this device for this use has not been demonstrated.

The BSD-2000 Hyperthermia System Essential Prescribing Information (EPI) is directed to the prescribing physician. For details concerning the operation of the device, please see the User Manual for the BSD-2000 Hyperthermia System.

BSD-2000 System Description

The BSD-2000 Hyperthermia System delivers localized therapeutic heating (hyperthermia) to solid tumors by applying radiofrequency (RF) energy at the frequency range of 75 to 120 MHz.

The BSD-2000 delivers energy to a patient using a power source and an array of multiple antennae that surround the patient's body. The BSD-2000 creates a cylindrically convergent radiated wavefront that utilizes the principles of constructive and destructive interference to create a central focusing of energy. Thus, the energy delivered by the BSD-2000 can be electronically focused to produce a localized power field that can be adjusted to target the 3-dimensional shape, size, and location of the tumor, thus providing dynamic control of the heating delivered to the tumor region. This method of therapeutic heating utilizes the adjustment of frequency, phase, and amplitude from multiple power sources, along with applicator selection and patient positioning, to optimize the deposition of heating energy into the targeted body tissues.

The BSD-2000 consists of four major subsystems: an RF power delivery subsystem; a proprietary, thermistor-based, thermometry subsystem; a computerized monitoring and control subsystem; an applicator subsystem that includes an applicator and patient support system; as well as various accessories, including a tissue equivalent QA lamp phantom that provides verification of the energy focus, pattern steering, and system operations. The BSD-2000 comes

in two configurations, a lower power basic system (BSD-2000B) that has a maximum power output of 1300 watts and an upgraded higher power system (BSD-2000U) that has a maximum power output of 1800 watts. The system includes a Sigma Base and applicators that are used inside of an enclosed RF shielded treatment area (not supplied by BSD Medical Corporation) in order to comply with FCC regulations.

Power Delivery Subsystem: A solid-state amplifier with 4-channel independent phase and amplitude adjustment capability with a maximum power output of 2000 watts (computer limited to a maximum of 1800 watts), 0 to 500 watts per channel. Each channel is monitored and controlled by the computer and can be individually adjusted for phase and amplitude. The computer monitors forward and reflected power, phase, and power on each channel.

Thermometry Subsystem: A set of non-perturbing, electromagnetically insensitive, temperature sensors with an accuracy of $\pm$0.2°C over a range of 25 to 52°C, are inserted into the patient using standard, sterile, disposable, closed-tip, insertion catheters (not furnished by BSD). Thermal mapping is an automated positioning system that allows the operator to map the sensor tip along the length of the catheter in order to determine the temperature profile.

Applicator Subsystem: The Sigma applicators (Sigma 60 and Sigma 60 Ellipse) are annular phased array applicators that are comprised of a clear plastic shell, 8 radiating dipoles, and a bolus membrane. The 8 dipoles are evenly spaced around the inside of a clear plastic shell and are oriented so that the radiated electric field is dominantly aligned with the central axis of the patient's body. The software automatically restricts the frequency range to 75-120 MHz for the Sigma 60 and 80-120 MHz for the Sigma 60 Ellipse.

Applicator and Patient Support System: The Sigma Treatment Base is part of the applicator subsystem and includes both the patient and applicator support system. A water system in the base is used to fill the bolus and to control the bolus water temperature. During treatment, the patient lies in a prone position on a fabric sling inside the applicator. The applicator is positioned over the tumor area and deionized water is pumped into the bolus to fill the space between the patient and the shell.

Computer Control System: An operator console containing computer controls to obtain and display data from the temperature sensors; to control the treatment power amplitude and temperatures using a closed-loop feedback system; and to record, display, and print relevant patient treatment parameters. Treatment parameters, including power output, frequency, amplitude and phase, tissue temperatures, core temperature, and treatment time are monitored and controlled by the Computer Control System, based on operator specified parameters. The System includes software pre-treatment planning programs that provide basic qualitative guidance, based on Specific Absorption Rate (SAR) testing, of the heating effects in the body.

Indication for Use

The BSD-2000 Hyperthermia System is intended for use in conjunction with standard radiotherapy for the treatment of cervical carcinoma patients who would normally be treated

with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors.

Procedure for Administration of Hyperthermia in Conjunction with Ionizing Radiation Therapy

Hyperthermia is administered during the delivery of standard radiotherapy, typically once per week, to a total of 5 treatments. The patients can be given Zanex 30 minutes prior to the treatment. The treatment objective is to deliver hyperthermia for 60 minutes after interstitially measured tumor temperature have reached a minimum of 42°C, or for a maximum total duration of 90 minutes. When temperatures of 42°C are reached in one or more locations inside the tumor, or after 30 minutes, the 60 minute hyperthermia treatment time period begins. The temperature elevation for normal tissues should be limited to 43°C, with the exception of subcutaneous fat tissue situated >1 cm from the skin, where 44°C is acceptable.

Contraindications

- Patients who have implanted, worn or carried medical devices, including cardiac pacemakers, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, radiofrequency identification devices attached to devices, or any other implanted active electronic device or monitoring system
- A body diameter >49 cm from left to right
- Severe dysfunction of the heart or lungs
- Severe pulmonary disease with a forced expiratory volume (FEV) <50%
- Patients who cannot adequately respond to pain (those with significant neuropathies)
- Patients who have had prior irradiation to the treatment site
- Patients who are less than 21 years of age
- Known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause)
- Patients who have electrically conductive, metal, or foreign objects in or on or attached to their body
- Unstable angina pectoris (under medication) with imminent threat of an infarction
- Myocardial infarction <6 months ago
- Cardiac decompensation necessitating medication
- Arrhythmia necessitating medication
- Heart rate >90bpm
- Hypertension: diastolic >100 mmHg and/or systolic >180 mmHg, while using medication
- Hypotension: diastolic <50 mmHg and / or systolic <90 mmHg
- Severe cerebrovascular disease: multiple cerebrovascular accidents (CVA) or a CVA <6 months before treatment
- Inability to place either an intratumoral or an intraluminal temperature sensor for monitoring of tumor indicative temperatures

Warnings

Clinical Warnings

Hyperthermia treatment with the BSD-2000 can significantly increase the whole body temperature of the patient. A Vital Signs Monitor (VSM), not supplied by BSD, must always be used during treatments with the BSD-2000 System to monitor the patient's vital signs. Emergency cardiopulmonary resuscitation and hypothermia inducing supplies should be readily available during treatments.

Systemic heating over 40°C may induce a general thermo-regulatory response exceeding the patient's compensatory capabilities and may cause injury to sensitive organs such as liver or brain.

Hyperthermia treatment should not be delivered if the patient's heart rate prior to start of treatment is >90 bpm or if patient's Systolic Blood Pressure (BP) is: >140 mmHg or <100 mmHg or diastolic BP is: >90 mmHg or <60 mmHg.

The following vital signs dictate reduction of applied power and/or cessation of treatment:

- Pulse >160
- Blood Pressure:
    - Systolic > 180 mmHg – diastolic > 100 mmHg
    - Systolic < 90 mHg – diastolic < 50 mmHg

If adequate blood flow is not present within the normal tissue located near the tumor area, excessive heating of the normal tissue may occur. Hyperthermia should not be used on patients with decreased circulation, which may be caused by vasoconstrictive drugs, disseminated intravascular coagulation (a blood clotting disorder), ischemia or other medical condition. Reduced blood flow can occur in areas that have scar tissue from surgery or in organs that contain stagnant fluid, such as the urinary bladder. If these types of tissues are located near the tumor area, an invasive temperature sensor can be placed to monitor heating in the normal tissue areas located near the targeted treatment area.

Large thermal doses (a continued elevation of moderately high temperature or a short extreme elevation of temperature) in normal tissue situated in the vicinity of the treated tumor or between the tumor and the body surface may result in regions of thermal aseptic necrosis that require medical intervention and that may not be apparent on inspection of the skin.

The BSD-2000 System temperature sensors and the invasive E-Field sensor are not sterile and must be inserted into tissue using a closed-end catheter to prevent infection. Temperature sensors must never be inserted directly into the tissue.

The depths at which temperature sensors must be placed for hyperthermia frequently require that monitoring sites be locally anesthetized prior to treatment for catheter insertion. However, when administering hyperthermia treatments, the use of analgesics and tranquilizers is appropriate

when needed, but under no circumstance is a general anesthesia or regional block to be used. Most agents used for anesthesia are derivatives of the 'caine' group of drugs, and caine derivatives are heat sensitizers and should be avoided during hyperthermia treatment.

Caution should be taken when working around the head and neck area of the patient to avoid exposing the eyes to stray EM energy.

The energy from the BSD-2000 System and applicators used with the system can present a risk to patients and to operators. Individuals who have a pacemaker or other active device implants or a metallic implant should not be inside the shielded treatment chamber during RF power output at any level. To prevent RF power output interference with active device implants, always leave the interlock door open when any individual who has an active device that is implanted, worn or carried is inside the shield room.

Metallic implants that are located in or on or attached to the patient's body may be excessively (and preferentially) heated or may contribute to excessive heating of the tissues contacting the metal implant or the electrical conductors and this may cause severe burns and patient injury.

A filled bolus contains a large volume of water that could cause the silicone bolus membrane to quickly tear if punctured. The water would then be released onto the patient. Because of this possibility, all punctures to the bolus membrane must be repaired immediately.

The bolus membrane can rupture while in use. The physician should ensure the sterility of the treatment surface if, in their medical judgment, it is necessary. It is BSD Medical's recommendation that any body hair that may press into the bolus membrane be removed prior to treatment.

Equipment/Electrical Warnings

Vital signs monitoring during hyperthermia treatment is restricted to heart rate, blood pressure, pulse, and core temperature using pneumatic measurement techniques. Cardiac monitoring devices, pulse oximeters, or other devices that utilize electrodes or wires should not be used during hyperthermia treatment as the energy from the BSD-2000 can interfere with the results and preferentially heat the electrodes and tissues in contact with the electrically conductive materials.

The energy from the BSD-2000 System and applicators used with the system can interfere with vital signs monitoring (VSM). The power output should be discontinued during monitoring of vital signs or the VSM electronics should be located outside of the shielded room.

Circuits in the BSD-2000 System are capable of electrical ignition of flammable liquids, anesthetics, gases, and vapors. The ignition of these materials can result in fires and/or explosions causing serious injury or death and/or property damage. Never operate the BSD-2000 System in the presence of flammable anesthetics or liquids and explosive gases or vapors. The possibility of relay contact arcing exists during operation that may ignite any flammable liquids, explosive gases, or vapors.

Burns can result from accidental contact with coaxial cables and connectors. Operators must not make adjustments to the cabling or connectors when EM energy is applied.

EM fields can cause heating of the body inside the shielded treatment room.
The E-fields should be measured to determine the potential exposure hazard. Levels over 1 mW/cm^2 should be avoided for periods of exposure over six minutes per hour for everyone except the patient. A hazard meter should be used to detect and monitor stray field levels.

To avoid possible electric shock while cleaning the BSD-2000 System, disconnect the system from the power source before cleaning its surfaces. Do not allow moisture to enter the electrical assemblies

The BSD-2000 System OFF control circuit can fail. If any light, monitor, or other visual indicator stays on after turning the system off, it is possible for any of the power-on hazards (electrical shock, electrical ignition, etc.) to exist. To prevent possible serious injury or death from any potential hazard, operator or service personnel must unplug the main power cable to the control console, amplifier, and other equipment.

Precautions

Adhere to the recommended procedures for temperature sensor placement and selection of control sensor. This will minimize the probability of excessive temperature in normal tissue or of inadequate treatment temperature in the tumor.

Cervical cancer treatments utilize temperature sensor(s) placed in catheters that have been inserted into natural orifices (intraluminal); i.e., rectum, urethra (bladder), and vagina, to estimate the regional temperature distribution. Published studies have demonstrated that the temperatures measured within a natural orifice that is adjacent to a tumor are representative of the temperatures obtained in the tumor. For cervical patients, vaginal temperatures are cervical tumor indicative; rectal and bladder temperatures are normal tissue indicative.

Interstitial or intratumoral thermometry may increase the risk of discomfort, pain, bleeding, severe infection, and tumor seeding. The procedure may also decrease patient tolerance and thus the ability to deliver the prescribed number of hyperthermia treatments. Thus, the ability to directly place temperature sensors in tumor and normal tissues may be limited.

Observe strict adherence to aseptic techniques during the invasive placement of temperature sensor insertion catheters. This will help to avoid infections. Instruct all patients in the daily care of indwelling catheters and sensor sites to prevent sepsis.

Verify calibration of temperature sensors daily, or as used, to ensure accurate temperature monitoring during treatments.

Adhere to recommended applicator placement and bolusing practices to reduce the likelihood of surface burns and blistering from the subsequent delivery of therapeutic heat.

Monitor closely physiological indicators of excessive heat delivery.

Cautions

Temperature sensors and the invasive E-Field sensor are not sterile and must be inserted into tissue using a closed-end catheter to prevent infection. Temperature sensors must never be inserted directly into the tissue.

Fluid spills on the equipment can cause severe equipment damage and/or serious injury or death due to electrical shock. Never place fluids on the BSD-2000 console. Use good judgment in protecting the equipment from fluids when treating a patient.

Damage to the bolus membrane will result if silicone grease lubricants are placed on the bolus membrane surface. Avoid staining the bolus membrane with iodines and Betadine.

Use caution when working with the bolus to prevent damaging the bolus membrane by impacts, puncturing, or localized stress.

The use of accessories, applicators, and cables other than those included with the BSD-2000, with the exception of applicators and cables sold by BSD Medical as replacement parts for internal components, may result in increased emissions or decreased immunity of the BSD-2000 System.

The BSD-2000 System should not be used adjacent to or stacked with other equipment. If the BSD-2000 is used with or stacked with other equipment, the BSD-2000, as well as the other equipment, should be tested to verify normal operation in the configuration in which it will be used.

If unauthorized maintenance of the BSD-2000 System should be performed, it is possible that there will be a significant change in the heating characteristics of the system and burns could result.

Operators must not remove the covers of the BSD-2000 System or attempt to perform any maintenance other than the periodic maintenance outlined in the *Maintenance Section* of the Operator Manual.

Do not use the equipment in an explosive atmosphere.

The BSD-2000 System uses voltages that are potentially lethal. Use extreme caution when performing maintenance of the BSD-2000 System.

Do not operate an electronic device or equipment emitting electromagnetic energy in proximity to the BSD-2000 System during a hyperthermia procedure, as the electronic equipment may interfere with the operation of the BSD-2000 System.

For pre-sterilized closed-tip insertion catheters, do not use if the integrity of the catheter package has been broken. For insertion catheters supplied without pre-sterilization, follow the manufacturer's sterilization recommendations. BSD does not supply insertion catheters.

The operator should NOT restore the system files or the registry information unless they are sure this data should be overwritten. Once restored, the old data is lost.

When handling the temperature sensors, the operator SHOULD NOT

- Touch the connector white plastic surface with your fingers
- Spill liquids at or near the connector sites
- Pull or stretch the temperature sensors
- Sharply bend or kink the temperature sensors
- Force a temperature sensor into a catheter

When handling the temperature sensors, the operator SHOULD:

- Properly align the sensor connector without applying force
- Handle temperature probes with care
- Store temperature sensors in a safe place when not in use
- Place the protective cap over the sensor connector when it is not connected to the temperature interface box

EM fields can cause heating of the body inside the shielded treatment room. The E-fields should be measured to determine the potential exposure hazard. Levels over 1mW/cm2 should be avoided for periods of exposure over six minutes per hour for everyone except the patient. A hazard meter should be used to detect and monitor stray field levels.

Remove large metal objects from the treatment room to prevent resonance excitation of these objects.

Keep all cables straight and free from entanglement and avoid use of rubber coated cables.

Pivotal Study – Overview

A Phase III, prospectively randomized study was conducted at Erasmus Medical Center – Daniel den Hoed Cancer Center (DHCC), Rotterdam, The Netherlands, from May 1, 1990, to September 1996. The study was conducted to compare hyperthermia (HT) and radiation (RT) to RT only treatment of locally advanced tumors of the cervix, bladder, and rectum. The primary endpoints of the study were local control and duration of local control. Secondary endpoints were acute toxicity, late toxicity, disease free survival and total survival. A total of 65 subjects were in the advanced cervical cancer subgroup. Of these 65 subjects, 33 were randomized into RT combined with HT and 32 patients were randomized into RT alone. This study met its primary endpoint of a 20% increase in complete response rates for cervical cancer patients receiving HT and RT as compared to RT alone.

Patients and Randomization. Advanced cervical patients were eligible for the trial if they required standard RT for cervical cancer International Federation of Gynecology and Obstetrics (FIGO) Stages IIB (with extension to the lateral parametrium), IIIB (fixation to the pelvic wall or ureter obstruction causing hydronephrosis), or IVA (invasion of the bladder or rectum). Patients needed to have a World Health Organization (WHO) performance status less than 2 and expected survival greater than 6 months. Absolute contraindications for a treatment with HT were a pacemaker, hip replacements or other metal implants with a dimension >10 cm, a body with a diameter >49 cm, and/or severe dysfunction of the heart or lungs.

Radiotherapy and Hyperthermia Treatment. RT was given per published international standards. HT was given once weekly, 4 hours after RT, to a maximum of 5 treatments. The patients were given Zanex 30 minutes prior to the treatment. The treatment objective was HT treatment for 60 minutes after interstitially measured tumor temperature had reached a minimum of 42°C, or for a maximum total duration of 90 minutes. A maximum induction period of 30 minutes was used to increase the tumor to intratumoral temperatures greater than 42°C. Treatment delivery settings were adjusted depending on observed temperatures and feedback from the patients. When temperatures of 42°C were reached in one or more locations inside the tumor, or after 30 minutes, the 60-minute HT treatment period began. The temperature elevation for normal tissues was limited to 43°C, with the exception of subcutaneous fat tissue situated >1 cm from the skin, where 44°C was acceptable.

Response Definition. Complete response (CR) was defined as disappearance of all viable tumor in the irradiated volume. Duration of pelvic tumor control was defined as either the time between the date of randomization and date of local progression within the irradiated volume or death from toxicity. Secondary endpoints were overall survival and toxic effects from RT or HT. Overall survival was defined as the time between randomization and death or last follow-up. Late toxicity (effects occurring ≥3 months after the last RT) was scored using the radiation morbidity scoring criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC).

Patient Population. There were 65 advanced cervical patients referred to as the BSD Intent-to-Treat ("BSD ITT") population. Of the 65 patients in the BSD ITT population, 33 were randomized into RT + HT and 32 patients were randomized into RT alone. Eighty-two percent (82%) of the advanced cervical cancer patients had FIGO Stage IIIB or IVA tumor, 70% had positive pelvic lymph nodes on CT scan, and tumor diameter was 6 cm or larger in 65%. Almost all patients with cervical tumors had irresectable tumors. No patients with cervical tumors had metastases present. Few patients (<10%) with cervical tumors had surgery prior to treatment. Their median age was 53 years, a large portion of patients had pathologically enlarged lymph nodes, and those patients with a FIGO stage IIB tumor all had tumor extension near the pelvic sidewall, all prognostic indicators that are associated with a poorer outcome for cervical cancer. The distribution of prognostic factors was balanced equally over the two treatment groups.

Eligibility for chemotherapy was not specifically assessed as part of patient demographics. However, given that renal failure and poor physical condition are often considered contraindications to chemotherapy, it is reasonable to assume that many DHCC study patients

would not qualify for chemotherapy. Specifically, due to the pattern of local extension of cervical cancer and the advanced state of the disease in many study patients, it is likely that many study subjects would have urethral obstruction and secondary renal failure that would have constituted a contraindication to chemotherapy.

Baseline Data. The subjects included in this analysis included 65 Intent-to-Treat (ITT) BSD-2000 subjects. The randomization was well balanced with 33 HT + RT subjects and 32 RT subjects.

Table 1 summarizes the baseline parameters.

Table 1. Baseline Summary, BSD ITT Population (n=65)

Parameter	Category or Statistic	Cervical RT	Cervical RT+HT
Sex n(%)	F	32 (100%)	33 (100%)
	M	0	0
Age (yr)	N	32	33
	Mean±SD	53.3±13.0	53.2±13.2
	Median	50.5	55.0
	Min,Max	30,82	29,75
WHO Performance Score n(%)	0	27 (84%)	25 (76%)
	1	5 (16%)	8 (24%)
	2	0	0
	3	0	0
Tumor Stage n(%)	Irresectable	30 (94%)	32 (97%)
	Recurrent	2 (6%)	1 (3%)
Tumor Stage n(%)	Missing	0	0
	T2	0	0
	T2b-lat	6 (19%)	6 (18%)
	T3	0	0
	T3b	22 (69%)	22 (67%)
	T4	4 (13%)	2 (6%)
	T4a	0	3 (9%)
	T4b	0	0
Maximum Tumor Diameter n(%)	Missing	0	0
	<=60mm	11 (34%)	12 (36%)
	60-80mm	11 (34%)	7 (21%)
	>80mm	10 (31%)	14 (42%)
Maximum Tumor Diameter (mm)	N	32	33
	Mean±SD	73.9±23.4	78.7±20.2
	Median	70.0	80.0
	Min,Max	30,150	45,130
Nodal Status n(%)	Missing	0	0
	N0	29 (91%)	28 (85%)

	N1	3 (9%)	5 (15%)
	N2	0	0
	Yes	1 (3%)	3 (9%)
Histology n(%)	Missing	0	0
	Adenocarcinoma	4 (13%)	2 (6%)
	Squamous Cell Carcinoma	27 (84%)	29 (88%)
	Transitional Cell Carcinoma	0	0
	other	1 (3%)	2 (6%)
Grade n(%)	Missing	5 (16%)	6 (18%)
	Good	2 (6%)	2 (6%)
	Moderate	16 (50%)	11 (33%)
	Poor	9 (28%)	13 (39%)
	No Diff.	0	1 (3%)

Treatment Summary. For the BSD ITT population, the median RT dose was about 65.5 Gy for both treatment arms administered over a median of about 50 to 51.5 days for cervical subjects across both treatment arms. One patient in the RT arm received HT therapy (per patient request). The percentage of cervical patients in the RT + HT arm who received less than five sessions of HT was 42% (cervical), though 63% received four or five sessions.

Pivotal Study – Safety Results

The side effects observed in the pivotal study were generally self-resolving or managed conservatively. There were no unanticipated safety considerations reported from the pivotal study. In the BSD ITT Population, 30/33 (91%) of the subjects in the radiation therapy (RT) + hyperthermia (HT) arm had at least 1 acute adverse event while 28/31 (90%) of the subjects in the RT arm did. There is no difference between the RT arm and the RT + HT arm. There is no difference between the RT arm and the RT+HT arm for side effects (see **Table 2**).

Burns and Fat/Muscle Necrosis/Induration: Burns are a known side effect of hyperthermia but deep hyperthermia patients do not usually experience surface burns. Instead, they experience subdermal burns that can result in fat or muscle necrosis or induration. Only one subject out of 33 (3%) had an acute skin HT effect (ulceration). Twenty (20) subjects (out of 117) had a subcutis HT effect; 4 had induration with tenderness lasting less than 24 hr, 15 had induration with tenderness lasting from 1-7 days, and 1 had induration with tenderness forcing postponement of a subsequent treatment.

Acute Skin RT Side Effects: There were 46/65 (71%) subjects with acute skin RT side effects, 22/32 (69%) in the RT arm and 24/33 (73%) in the RT+HT arm. Effects appear similar between the RT and RT+HT arms. Nineteen (19) (out of 65) (29%) had erythema, dry desquamation, 26/65 (40%) had severe/painful erythema, some epidermolysis, slight edema, 1/65 (<1%) had confluent epidermolysis also outside skin folds, pitting edema. The addition of HT to RT did not increase the acute skin side effects from RT, as compared to RT alone.

Small Intestine Side Effects: There were 33/65 (51%) subjects with small intestine side effects, 17/32 (53%) in the RT arm and 16/33 (48%) in the RT+HT arm. There is no apparent difference between RT and RT+HT for small intestine effect. The addition of HT to RT did not increase the small intestine side effects, as compared to RT alone.

Large Intestine Side Effects: There were 24/65 (37%) with large intestine side effects, 9/32 (28%) in the RT arm and 15/33 (45%) in the RT+HT arm. There were 27/65 (42%) with change in stool frequency, no medication required, and 24/65 (37%) with change in stool frequency or pain, medication required. There is a minimal difference between RT and RT+HT for large intestine effect.

Bladder Side Effects: There were 31/65 (48%) with bladder side effects, 15/32 (47%) in the RT arm and 16/33 (48%) in the RT+HT arm. There is no apparent difference between RT and RT+HT. Twenty-four (24) (out of 65) (37%) had frequency twice pretreatment value, dysuria, no medication required, and 7/65 (11%) had frequency<1/hr, dysuria, spasms, requiring medication. The addition of HT to RT did not increase the bladder side effects, as compared to RT alone.

Pain: Pain was not reported as an adverse effect during the study. However, reported rates in published studies of localized and temporary pain in the area of, and during delivery of, therapeutic heat using the BSD-2000 have varied from 0-60%. The pain could be controlled and ended when power was turned off.

Other Side Effects: There have been other adverse reactions reported in published studies using the BSD-2000 that were not observed in the pivotal study. Catheter toxicity/infection and ulceration (usually attributed to tumor necrosis) was reported in fewer than 10% of the subjects. A few subjects or a single subject only reported other adverse reactions, which may or may not have been hyperthermia related, which included: osteonecrosis, tumor growth along the thermometry catheter track, peripheral neuropathy, numbness, cramping, peptic ulcer, hypotension, diarrhea, dermatitis, edema, tingling, acute mucitis, dysuria, claustrophobia, cardiac stress, bradycardia/syncope, and hematuria.

Table 2 summarizes the number of subjects who had any reported acute adverse event in the BSD ITT Population, excluding only 1 subject with all acute adverse event data missing. **Table 3** summarizes the safety data for the BSD ITT population. Six (out of 65) patients had less RT than planned, 5/32 (16%) were in the RT arm and 1/33 (3%) were in the RT + HT arm. One was for general poor condition, 1 was according to plan, and 4 were due to disease progression outside of the treatment volume.

Table 2. Any Acute Adverse Event Summary, BSD ITT Population with Adverse Event Information (n=64)

Group	No AE	At Least One AE
Cervix RT	3 (10%)	28 (90%)
Cervix RT+HT	3 (9%)	30 (91%)

Table 3. Safety Summary (n=65)

Parameter	Category	Cervical RT	Cervical RT+HT
Skin RT effect acute	Missing	2 (6%)	0
	None	8 (25%)	9 (27%)
	Erythema, Dry Desquamation	8 (25%)	11 (33%)
	Severe/Painful Erythema, Some Epidermolysis, Slight Edema	13 (41%)	13 (39%)
	Confluent Epidermolysis also Outside Skin Folds, Pitting Edema	1 (3%)	0
Skin HT effect acute	Missing	32 (100%)	4 (12%)
	None	0	28 (85%)
	Ulceration	0	1 (3%)
Subcutis HT effect acute	Missing	32 (100%)	4 (12%)
	None	0	26 (79%)
	Induration with Tenderness<24 hr	0	1 (3%)
	Induration with Tenderness 1-7 days	0	1 (3%)
	Induration with Tenderness, Postponement of Subsequent Treatment	0	1 (3%)
Small intestine effect (acute)	Missing	1 (3%)	0
	None	14 (44%)	17 (52%)
	Anorexia <5% Weight Loss, Nausea or Abdominal Discomfort, No Medication Required	11 (34%)	13 (39%)
	Anorexia 5-15% weight loss, nausea or abdominal discomfort requiring medication	6 (19%)	3 (9%)
	Anorexia >15% weight loss, nausea/vomiting insufficiently responding to medication, hematemesis/melena	0	0
Large intestine effect (acute)	Missing	1 (3%)	0
	None	6 (19%)	7 (21%)
	Change in stool frequency, no medication required	16 (50%)	11 (33%)
	Change in stool frequency or pain, medication required	9 (28%)	15 (45%)
	Diarrhea requiring parenteral support, rectal discharge requiring use of bandages	0	0
	(Sub)Acute obstruction, fistula or perforation, bleeding requiring transfusion, surgical intervention	0	0
Bladder (acute)	Missing	1 (3%)	0

Parameter	Category	Cervical RT	Cervical RT+HT
	None	16 (50%)	17 (52%)
	Frequency twice pretreatment value, dysuria, no medication required	11 (34%)	13 (39%)
	Frequency<1/hour, dysuria, spasms, requiring medication	4 (13%)	3 (9%)
	Frequency>=1/hr, dysuria, painful spasms requiring medication, macroscopic hematuria	0	0
	Hematuria requiring transfusion, bladder obstruction, ulceration or necrosis	0	0
Cause of death	Missing	13 (41%)	18 (55%)
	Locoregional Recurrence	8 (25%)	5 (15%)
	Distant Metastases	4 (13%)	5 (15%)
	Intercurrent	1 (3%)	1 (3%)
	Complications	1 (3%)	1 (3%)
	Locoregional Disease and Metastasis	5 (16%)	3 (9%)
Months until late toxicity ≥3	Missing	8 (25%)	2 (6%)
	3 - < 6 mo	3 (9%)	2 (6%)
	6 - < 9 mo	4 (13%)	8 (24%)
	9 - < 12 mo	3 (9%)	0
	12 - < 18 mo	5 (16%)	7 (21%)
	18 - < 24 mo	3 (9%)	3 (9%)
	24 - < 36 mo	3 (9%)	4 (12%)
	>= 36 mo	3 (9%)	7 (21%)
Max grade during follow-up	Missing	8 (25%)	2 (6%)
	0	14 (44%)	18 (55%)
	1	6 (19%)	6 (18%)
	2	2 (6%)	2 (6%)
	3	1 (3%)	3 (9%)
	4	1 (3%)	1 (3%)
	5	0	1 (3%)

Two cases of fatal necrosis of the lesser pelvis were reported for patients two and three years after receipt of combined radiotherapy and hyperthermia using the BSD-2000 for cervical carcinoma treatment, a severe adverse event not reported with any other patients who have received hyperthermia and radiotherapy. One of these patients was included in the pivotal study; an autopsy determined that the cause of death for this patient was local tumor progression. An autopsy was not performed on the patient not included in the pivotal study. The contribution, if any, of hyperthermia to this severe side effect, though unlikely, could not be completely eliminated.

Potential Side Effects

The following adverse effects might be expected (potential), but have not yet been observed in the completed and ongoing clinical studies of the BSD-2000.

Exacerbation of pre-existing disease. Patients having borderline cardiopulmonary function secondary to coronary atherosclerosis, emphysema, or other conditions, may not be able to tolerate the additional systematic stress of extensive or prolonged hyperthermia.

Enhanced drug activity. Elevated temperatures may be expected to affect the pharmacologic activity of some drugs, with unpredictable results. Altered vascular perfusion may dramatically affect the local tissue effects of systemic or infused drugs.

Thermal Stress. Significantly increasing the core temperature of the body or overheating the thermo-regulatory center in the brain may result in thermal stress exceeding the patient's compensatory mechanisms. Reliable prediction of the consequences of thermal stress in patients with cardiovascular impairment is not possible. Signs of consequences of thermal shock or of local brain overheating may appear after several (up to 24) hours.

Pivotal Study – Effectiveness Results

Local control or complete response was the primary study endpoint. Local control or complete response (CR) was defined as no evidence of tumor tissue within the irradiated tissue volume. Patients were not assessable for tumor control if their death occurred within 3 months after the end of the treatment. Patients who did not show complete response were classified as local-treatment failures at day 0. Time to local failure was defined as the time between randomization and date of local progression in the irradiated volume, or death because of toxicity. Duration of complete response (CR) was defined as date of regression minus date of CR if there was regression, or date of last contact minus date of CR if there was no regression. For the analysis, duration was censored at 36 months.

Table 4 summarizes the complete response frequencies, odds of not having a complete response for each treatment arm, the odds ratio, and the statistical analysis from the contingency table for the BSD ITT population. The odds of not having a complete response were calculated for each tumor site by treatment arm. The odds ratio was calculated as the odds of the RT + HT treatment divided by the odds of the RT treatment. Thus, an odds ratio less than one indicates that RT+HT treatment has a higher proportion of complete response than does the RT treatment.

For the BSD ITT population, 29/33 (88%) of the RT+HT arm had CR, 18/32 (56%) of the RT arm had a CR, for an odds ratio=0.1773 (95% confidence interval 0.0504, 0.6235) and the difference between treatments was statistically significant (p=0.006, Fisher exact test). This result corresponds to a much lower failure rate in the RT + HT subjects.

Table 4. Complete Response Analysis, Odds Ratio, BSD ITT Population (n=65)

Complete Response	RT+HT	RT	Total	Chi Square p-value	Fisher Exact p-value	Odds Ratio	95% Lower CL Odds Ratio	95% Upper CL Odds Ratio
No	4 (12%)	14 (44%)	18 (28%)	0.010	0.006	.	.	.
Yes	29 (88%)	18 (56%)	47 (72%)	.	.	.	.	.
Total	33	32	65	.	.	.	.	.
Odds of No CR	0.14	0.78		.	.	0.1773	0.0504	0.6235

Complete Response Duration

Table 5 summarizes the duration of complete response for the BSD ITT Population. There is no statistical difference between treatments. Thus, patients who had a complete response maintained the complete response for the same length of time regardless whether they were in the RT + HT arm or in the RT arm.

Table 5. Duration of Complete Response, BSD ITT Population with CR (n=47)

	Cervical RT	Cervical RT+HT
Number Patients with CR	18	29
Duration <36 mo and had progression	2	8
Censored Duration < 36 mo	15	15
Duration >= 36 mo	1	6
p-value*	0.44	

*p-value from log rank survival analysis

Complete Response by Tumor Stage (Irresectable / Recurrent)

Table 6 summarizes the complete response rates by treatment and tumor stage (irresectable/recurrent). The cervical tumors were almost all irresectable. The complete response rate is substantially higher for the RT + HT treatment (91%) than it is for the RT treatment (57%).

Table 6. Complete Response by Tumor Stage (Irresectable/Recurrent), BSD ITT Population (n=65)

Tumor Stage	Complete Response	RT+HT	RT	Total
Irresectable	No	3 (9%)	13 (43%)	16 (26%)
	Yes	29 (91%)	17 (57%)	46 (74%)
	Total	32	30	62
Recurrent	No	1 (100%)	1 (50%)	2 (67%)
	Yes	0 (0%)	1 (50%)	1 (33%)
	Total	1	2	3

Tables 7 (by tumor stage) and **8** (by tumor diameter) summarize the effects in the cervical tumor model. The data show the advanced stage of disease presented by the cervical patients. Eighty-two percent (82%) had a FIGO Stage IIIB or IV tumor and 65% had a tumor size greater than 6 cm. The complete response rate for RT+HT was 29/33 (88%) while it was 18/32 (56%) for RT. The complete response rate was higher for T2b (11/12 (92%)) than for T3b (32/44 (73%)) than for T4 and T4a (4/9 (44%)). The complete response rate was slightly higher for tumors of smaller diameter than for tumors with a larger diameter, ≤60 mm had a complete response of 17/23 (74%), 60-80 mm had a complete response rate of 13/18 (72%), >80 mm had a complete response rate of 17/24 (71%), and the natural conclusion is that the effect of tumor diameter is minimal.

Table 7. Complete Response, Cervical Tumors by Treatment by Tumor Stage (T2 etc.), BSD ITT Population (n=65)

Treatment	Complete Response	T2b	T3b	T4	T4a	Total
RT+HT	No	0	2 (9%)	1 (50%)	1 (33%)	4 (12%)
	Yes	6 (100%)	20 (91%)	1 (50%)	2 (67%)	29 (88%)
	Total	6	22	2	3	33
RT	No	1 (17%)	10 (45%)	3 (75%)	0	14 (44%)
	Yes	5 (83%)	12 (55%)	1 (25%)	0	18 (56%)
	Total	6	22	4	0	32
Total	No	1 (8%)	12 (27%)	4 (67%)	1 (33%)	18 (28%)
	Yes	11 (92%)	32 (73%)	2 (33%)	2 (67%)	47 (72%)
	Total	12	44	6	3	65

Table 8. Complete Response, Cervical Tumors by Treatment by Tumor Diameter, BSD ITT Population (n=65)

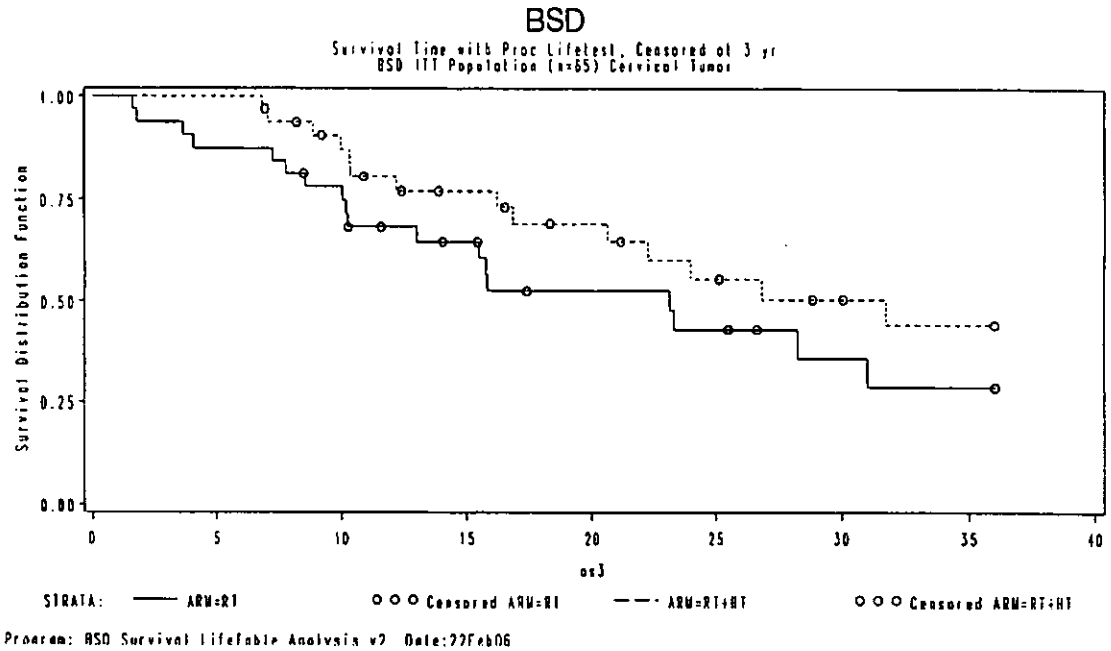
Treatment	Complete Response	<=60 mm	60-80 mm	>80 mm	Total
RT+HT	No	1 (8%)	0	3 (21%)	4 (12%)
	Yes	11 (92%)	7 (100%)	11 (79%)	29 (88%)
	Total	12	7	14	33
RT	No	5 (45%)	5 (45%)	4 (40%)	14 (44%)
	Yes	6 (55%)	6 (55%)	6 (60%)	18 (56%)
	Total	11	11	10	32
Total	No	6 (26%)	5 (28%)	7 (29%)	18 (28%)
	Yes	17 (74%)	13 (72%)	17 (71%)	47 (72%)
	Total	23	18	24	65

Three-Year Survival Analysis. Survival is a secondary endpoint. A life table analysis of survival was performed with those living longer than three years censored at three years. For the BSD ITT population, **Table 9** summarizes descriptively the number that died prior to three years, the number for which the last follow-up was less than three years and they were alive at the last follow-up, and those that were alive at three years. In the BSD ITT population, 14/33 (42%) of the RT+HT patients and 18/32 (56%) of the RT patients died prior to three years. The median survival times were 31.7 months for the 33 patients in the RT+HT group and 23.2 months for the 32 patients in the RT group. There was no statistical difference between the treatments (p-value=0.16, log rank test), and the survival curves are slightly separated. Survival curves for BSD ITT population cervical patients are in **Figure 1**.

Table 9. Three-Year Survival Summary, BSD ITT Population (n=65)

Overall Survival Category	RT+HT	RT	Total
Died prior to 36 mo	14 (42%)	18 (56%)	32 (49%)
Alive, censored prior to 36 mo	12 (36%)	10 (31%)	22 (34%)
Alive at 36 mo	7 (21%)	4 (13%)	11 (17%)
Total	33	32	65
Median Survival (mo)	31.7	23.2	
p-value		0.16	

Figure 1. Survival Time for Cervical Tumor Patients, BSD ITT Population (n=65)



The addition of HT to RT demonstrated a statistically significant improvement (p=0.006, Fisher exact test, BSD ITT Population) in local tumor control for cervical cancer. The CR rate for RT+HT was 88%, whereas it was 56% for RT. In the BSD ITT population, 14/33 (42%) of the RT + HT patients and 18/32 (56%) of the RT patients died prior to three years. The median survival times were 31.7 months for the RT + HT group and 23.2 months for the RT group. There was no statistical difference between the treatments (p-value=0.16, log rank test). The addition of the HT increased the survival time by 8.5 months. Even though there was a trend towards increased survival for the patients treated with the BSD-2000, the difference was not statistically significant (p=0.71, log rank survival) for the BSD ITT Population. Given the statistically significant improvement in local tumor control, the lack of statistical significance in three-year survival may simply reflect the number of patients on which this analysis is based. In addition to these pivotal study data, 12-follow-up data has been published on the same 65 patient cohort described in the pivotal study. These results do not achieve statistical significance in the BSD-2000 ITT population. However, this lack of significance may be due to relatively low patient numbers, together with the high long-term mortality rate generally seen in patients with advanced cervical carcinoma. **Tables 10** and **11** summarize these data.

In this extended follow-up, side effects for HT were few and generally self-resolving and mild. There were no severe or unexpected toxicities or late effects that were attributed to the BSD-2000 treatment.

Table 10. Twelve-Year Survival Summary, BSD ITT Population (n=65)

Tumor Type	Overall Survival Category	RT+HT	RT	Total
Cervix	Alive at 12 years	3 (9%)	2 (6%)	5 (8%)

	Died prior to 12 years	24 (73%)	23 (72%)	47 (72%)
	Censored prior to 12 years	6 (18%)	7 (22%)	13 (20%)
	Total	33	32	65
	Median Survival (mo)	2.2	1.9	
	Log-Rank Test p-value	0.3589		

Table 11. Twelve-Year Survival Summary, Non-BSD Population (n=49)

Tumor Type	Overall Survival Category	RT+HT	RT	Total
Cervix	Alive at 12 years	7 (28%)	2 (8%)	9 (18%)
	Died prior to 12 years	12 (48%)	20 (83%)	32 (65%)
	Censored prior to 12 years	6 (24%)	2 (8%)	8 (16%)
	Total	25	24	49
	Median Survival (mo)	Not avail	1.6	
	Log-Rank Test p-value	0.0288		

Alternate Practices or Procedures

Three alternative cancer treatment methods are currently available to treat cervical cancer: surgery, radiation therapy, and chemotherapy. Some treatment approaches utilize two or more of these methods in combination. In addition, biological therapy is sometimes used for cancer treatment.

Recommended Abbreviated Instructions for a BSD-2000 Hyperthermia Procedure

Pretreatment Patient Preparation

- Insert sterile closed-tip, plastic/rubber catheters (not supplied by BSD), as needed, for invasive intratumoral and intraluminal temperature sensor placement. It is recommended that temperature sensors be placed in or near the target tumor tissue as well as in natural body cavities that are close to the target area to be heated. A temperature sensor should be placed in the vagina for monitoring of tumor indicative temperatures. Temperature sensors can also be placed in the tumor for direct monitoring of tissue temperature. Additional temperature sensors can be placed in the rectum and bladder for monitoring of normal tissue indicative temperatures in the targeted area.
- Start prophylactic antibiotic regimen one day prior to catheter insertion.
- Fleet enema, if required. (Patient should self-administer approximately 2 to 3 hours prior to treatment.)
- Give patient prescribed pain medication and/or oral relaxant at least 45 minutes prior to treatment or as prescribed by physician.

- Have patient empty bladder before starting the procedure or place a urethral catheter to drain urine from bladder during treatment.

Pretreatment Equipment Preparation

- Select the bolus water temperature using the temperature dial; select the HEAT mode. Warm the water for at least 60 minutes prior to the treatment to a temperature between 25 to 30°C to improve patient comfort.
- Slide the Sigma Applicator to the patient's foot end of the base and center the Patient Support Pad under the sling assembly.
- Turn on the BSD-2000 Console main power switch.
- Determine the initial RF power settings for amplitude, balance, frequency, and phase steering using the Pretreatment Planning program or equivalent method.
- Select Sensor Calibration on the Main Menu screen and perform the temperature sensor calibration or verification procedure.
- Select Hyperthermia Treatment from the BSD-2000 Main Menu screen.
- Select either New Patient and enter the patient's name or number, or, for previously treated patients, select the patient's file by name or number.
- Complete and verify the Treatment Description screen.
- Select the Icon for the appropriate Sigma applicator.
- Select the initial frequency, power amplitude balance, and phase steering parameters, according to the initial treatment planning calculations.

Treatment Setup

- Place the patient on the sling.
- Raise the patient sling and remove the support cushions.
- Adjust the patient elevation to center the patient vertically in the Sigma aperture.
- Slide Sigma applicator over patient and center approximately on target tumor location.
- Insert temperature sensors into previously placed catheters, as needed, for invasive temperature monitoring. Insert catheters and temperature sensors, as needed, for surface and natural orifice temperature monitoring. Monitoring of systemic temperatures throughout the treatment is encouraged. BSD recommends that a temperature sensor be placed under the patient's tongue every 30 minutes. A catheter (or equivalent protective device), must be used to prevent damage to the sensor.
- Place E-field sensors (if used).
- Connect vital signs monitor.
- Fill water bolus and carefully stretch out bolus folds on both sides of the patient by gently pulling on bolus edges.
- Once bolus is filled, start bolus circulation and adjust the water temperature thermostat to provide patient cooling (if desired).
- Start treatment immediately after bolus is filled to reduce patient time in applicator and thus reduce patient fatigue.

Treatment

- Select the Start Tx icon.
- Set the RF Power to ON and check that control and maximum temperature limits, frequency, amplitude, phase, and phase settings are set to the correct level.
- Start power output at 20% of the planned level and verify that the measured reflected powers are less than 20% of the forward power per channel, indicating the cables are connected and the bolus is filled.
- Assess comfort level.
- Begin patient vital signs monitoring.
- Verify that displayed power and phase measurements correspond to the settings.
- If E-field probes are used, verify that their measurements correlate with the predicted heating pattern.
- Gradually increase the maximum RF power setting to achieve a minimum tumor heating rate of 0.2°C per minute. (If the tumor temperature remains below 40°C after 30 minutes of heating, the patient may not be suitable for treatment.)
- During the heating period, regularly monitor the patient's vital signs, status and comfort level.
- If patient experiences discomfort that is described as pressure, cramping, dull pain, or irritation in the deeper tissues, temporarily reduce the total power until the patient no longer experiences discomfort.
- If patient experiences discomfort that is described as a superficial burning or a hot spot, reduce the power in the channel corresponding with the painful area.
- Monitor heart rate (HR) every 30 minutes, unless rate is >90 beats per minute (bpm), in which case monitor HR every 5 minutes until it falls to < 90 bpm, at which time resume monitoring every 30 minutes.
- Monitor blood pressure (BP) every 30 minutes unless systolic is > 140 mmHg or < 100 mmHg and/or diastolic is > 90 mmHg or < 60 mmHg, in which case monitor BP every 5 minutes until the systolic decreases to < 140 mmHg or > 100 mmHg and/or diastolic decreases to < 90 mmHg or > 60 mmHg, at which time resume monitoring every 30 minutes.
- Reduce power and/or cease treatment if the patient's pulse >160 or if the patient's BP is:
  - Systolic > 180 mmHg – diastolic > 100 mmHg
  - Systolic < 90 mmHg – diastolic < 50 mmHg
- Deliver the prescribed treatment protocol (Temperature and Time). The system will automatically disable RF Power once the operator selected Therapeutic Time has been reached.
- When the treatment period has been completed, disable the RF power if treatment has not been automatically stopped.

End of Treatment

- Drain the water bolus as soon as possible after the RF power has been turned off.
- Remove the E-field sensors, temperature sensors, and vital signs monitor.
- Slide Sigma Applicator to the patient's foot end of the Sigma Base.
- Raise the patient sling, if needed, and position the support pad under the patient.

- Lower the patient sling and poles so the patient is resting on the support pad.
- Assist the patient to sit up, provide support as needed, and allow adequate time for the patient to establish balance before standing.
- It is recommended that the patient be observed for up to one hour post treatment, or for the appropriate time period determined by the physician, to ensure the patient does not develop any subcutaneous blisters or burns that would need medical attention.
- Clean the patient contacting surfaces of the Sigma Applicator using mild water based soap or detergent. Clean the silicone bolus using alcohol but avoid getting the alcohol on the clear plastic tubing. (Do not use alcohol on the applicator surfaces.)
- Remove the fabric sling and launder the sling using mild soap (no bleach) and warm water temperatures. Tumble dry immediately using a no heat setting.
- Replace the patient sling on the Sigma Base.

Post Treatment Patient Instructions

- Post-treatment antibiotic, NSAID, and antispasmodic, if needed.
- Adequate fluid intake and a balanced diet.
- Follow-up appointment date.
- Contact physician if fever is >101.5°F (38.6°C), excessive bleeding or discomfort.
- Other patient care instructions as needed.

Patient Information

Patient labeling is available to assist the physician in counseling the patient about this device and the procedure. The patient labeling should be provided to the patient in a timely manner.

Patient Counseling

The BSD-2000 has a Humanitarian Device Exemption (HDE) approval for use in conjunction with radiation therapy in the treatment of cervical carcinoma patients who are ineligible for chemotherapy. An HDE approval means that the probable benefit to health of the device outweighs the risk of injury or illness from its use. However, the effectiveness of this device for its intended purposes has not been established. The prescriber should disclose to the prospective patients that the effectiveness of the BSD-2000 has not been demonstrated but that there are limited clinical data of a qualitative nature that suggest benefit. The BSD-2000 is not an alternative to chemotherapy treatment for advanced cervical cancer. Chemotherapy has been proven to be effective for improving survival, whereas hyperthermia has not.

Patient
LABELING

Patient Brochure for the

BSD-2000 Hyperthermia System

BSD Medical Corporation
2188 West 2200 South
SLC, UT 84119
Phone: (801) 972-5555
FAX: (801) 972-5930
Website: www.bsdmc.com

Part No:
Revision:

Patient Brochure for BSD-2000 Hyperthermia System

Table of Contents **Page No.**

Humanitarian Use Device. Authorized by Federal law for use in the treatment of cervical carcinoma patients who would normally be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors.

The effectiveness of the BSD-2000 Hyperthermia System for treatment of advanced cervical cancer has not been demonstrated. The BSD-2000 has a Humanitarian Device Exemption (HDE) approval for use in conjunction with radiation therapy in the treatment of cervical carcinoma patients who would normally be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors. An HDE approval means that there are limited clinical data that suggest benefit and these data show that the probable benefit to health of the device outweighs the risk of injury or illness from its use. However, the data did not prove that there was any benefit from adding hyperthermia to radiation treatment. The BSD-2000 is not an alternative to chemotherapy treatment for advanced cervical cancer. Chemotherapy has been proven to be effective for improving survival, whereas hyperthermia has not.

About This Brochure

This brochure tells you about how hyperthermia is used to treat some types of cancerous tumors using the BSD-2000 System. The brochure also tells you what to expect, the preparations necessary, and the possible side effects of the treatment. Hyperthermia is only done under the care of a doctor and is usually performed in the radiation oncology department of a hospital. Your doctor can answer any questions you may have about how hyperthermia works and how it will be incorporated into your overall treatment program.

What is BSD-2000 Hyperthermia?

Hyperthermia means "elevated or increased temperature". During a hyperthermia treatment, the cancerous tumor is heated up to a temperature between 40 and 45 °C (104 - 113 °F) for a period of time. Unlike healthy cells, cancer cells cannot tolerate these high temperatures. Thus, some cancer cells will be killed by the heat. The healthy tissue is usually not damaged.

Hyperthermia is used in combination with standard radiation treatment. Hyperthermia can make radiation treatment more effective. Hyperthermia is a "local" treatment, meaning the treatment only works on the targeted local tumor. Hyperthermia treatments, like radiation therapy, involve physicians, physicists, and technicians. You should discuss the details of your radiation treatments, and how it will be coordinated with the hyperthermia treatment, with your radiation oncologist.

Hyperthermia treatments are applied according to your physician's direction. The scheduling of the treatments depends on your radiation therapy schedule. Your physician will give you a hyperthermia treatment schedule before treatments begin.

How Does Hyperthermia Affect Tumors?

Hyperthermia kills some cancer cells by raising the tumor temperature to a "high fever" range, similar to the way the body uses fever naturally when fighting other forms of disease. Raising the tumor to a higher temperature also makes the cancer cells more likely to be killed by the radiation therapy and makes the tumor less able to recover from the effects of the radiation therapy. Thus, hyperthermia is a radiation sensitizer, which means it increases the effect of radiation. The addition of hyperthermia to radiation treatment is not expected to increase the side effects of the radiation therapy because the body is cooled by blood flow. For instance, when your hand or face gets hot, it turns red because the blood rushes to cool it down. This is the body's natural method for cooling down body parts. However, the blood flow in cancer tissue is slower than normal tissue. This makes the cancer tissue vulnerable to increased heating, even though the healthy tissue is not.

When the BSD-2000 Should Not Be Used

Your physician will consider many factors before recommending the BSD-2000 treatment for you. There are certain conditions that make a person ineligible for hyperthermia. Hyperthermia contraindications (indications against use) are listed below. BSD-2000 therapy should not be used for a patient with any of these conditions. For these patients, the risks are greater than the potential benefits.

Decreased Pain Response
Because a patient's ability to feel pain is an essential safety factor for hyperthermia treatment, hyperthermia is contraindicated in patients whose pain response has been significantly reduced by any means (such as previous surgery or radiation therapy to the treatment site, regional or general anesthetic, or other conditions, including patients with significant neuropathies; i.e., functioning of the nerves).

Decreased Circulation
Since excessive heating of normal tissue is prevented by normal blood flow, it is important that adequate blood flow be present and maintained in all normal tissues located near the heating field. Hyperthermia should not be used on patients with reduced blood circulation, which may be caused by vasoconstrictive drugs (which restrict the blood vessels), disseminated intravascular coagulation (a blood clotting disorder), ischemia (an insufficient supply of blood to an organ), or other medical conditions.

Active or Metal Implants
Hyperthermia should not be used on patients with pacemakers, metal implants (for example, hip or knee replacements), or other active medical devices that are implanted, worn or carried, including, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, or any other implanted active electronic device or monitoring system because hyperthermia may interfere with the operation of the active medical device and the metal implant may heat more quickly and to a higher temperature than other tissue.

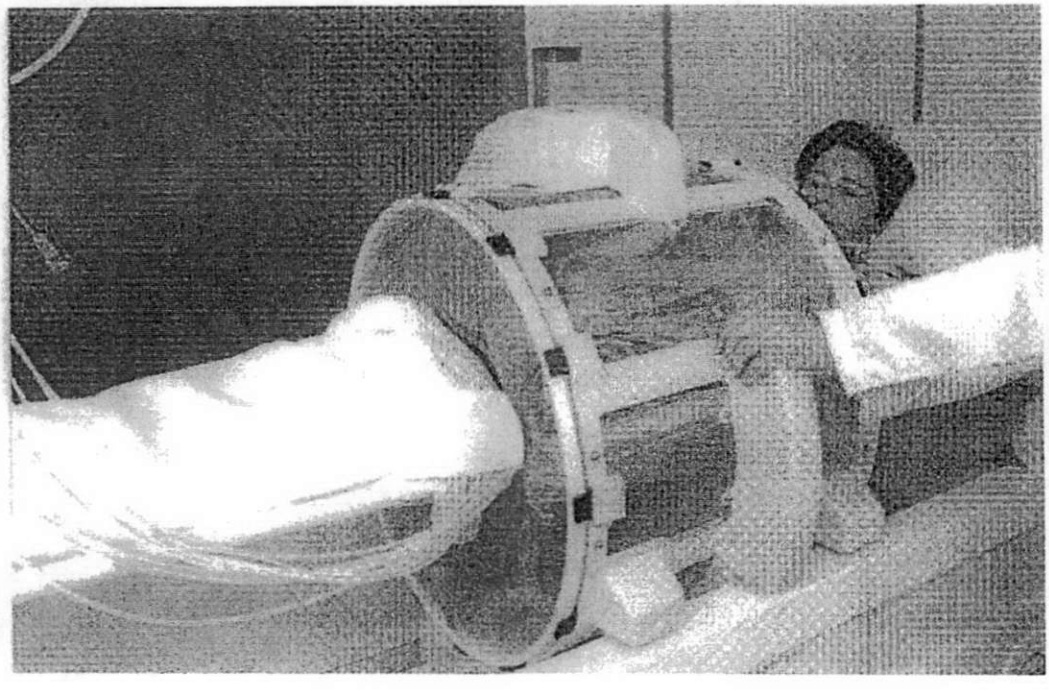
Weak Heart or Lungs
Hyperthermia may cause an increase in pulse and/or blood pressure, similar to an aerobic exercise workout. Thus, hyperthermia should not be used for patients with unstable angina, a heart attack or a stroke within the last 6 months, or significant pulmonary disease that requires supplemental oxygen.

What Are the Alternate Practices or Procedures?

Three alternative cancer treatment methods are currently available to treat cervical cancer: surgery, radiation therapy, and chemotherapy. Some treatment approaches utilize two or more of these methods in combination. In addition, biological therapy is sometimes used for cancer treatment. Biological therapy is used to stimulate the immune system.

What is the BSD-2000?

The BSD-2000 Hyperthermia System is used to deliver therapeutic (beneficial) heating (hyperthermia) to cancerous tumors by the use of radiofrequency (RF) energy (see photograph below). Therapeutic heating temperatures are temperatures that are greater than 40 °C. Radiofrequency (RF) energy generates the necessary heat to kill cancer cells. The BSD-2000 delivers RF energy to a patient using a power source and several antennas that surround the patient's body. The targeted region of the patient's body is enclosed within either a cylindrical or an elliptical shaped applicator that contains the antennas (*i.e.*, the devices that deliver the energy into the tumor). RF energy is invisible and is generally not harmful. When the RF energy enters the body, the targeted tumor location will get warm. The elevated temperature has a harmful effect on the tumor cells. The heating effect of the energy will stop as soon as the equipment is turned off.



The BSD-2000 is operated within an enclosed shielded treatment area to prevent interference of the RF energy with commercial broadcasting and/or other electronic equipment. A hyperthermia treatment area includes an enclosed treatment room (which contains the applicator) and the operator room (which contains the computer console and other equipment where the technologist directs the treatment).

You can discuss with your physician the possibility of bringing someone to your hyperthermia treatment sessions to keep you company during treatment. However, this person may not be allowed inside of the treatment room because of the potential harm from stray energy inside the treatment room. People with pacemakers, metal implants, prostheses, or other active medical devices cannot be allowed into the treatment room

because there is a chance their implants could malfunction. People with hearing aides should not be in the treatment room, because the proper function of the hearing aid can be inhibited or even damaged. Women who are pregnant should not be present during treatments as a precaution.

What Procedures Will Be Needed Prior To Treatment?

Before your treatment, you will have an appointment with your doctor. During the appointment, you may need to undergo several tests to see if hyperthermia is a potential treatment option for you. You should discuss these tests with your physician. Once it has been determined that hyperthermia is right for you, there are other procedures that you may undergo in preparation for actual treatment. The most common of these procedures are described below.

Catheters

During the hyperthermia treatment, the tissue is heated to a temperature between 40 and 45 °C (104-113 °F). The amount of energy needed differs from person to person, so the temperature during the hyperthermia treatments may be measured in several places in your body using temperature sensors. Temperature sensors are placed using catheters. A catheter is a small plastic tube that may be inserted inside the body, into body openings, for example, the vagina, rectum, bladder, or placed into the tumor tissue or on the skin. Thus, you may have catheters placed prior to your treatment.

In some cases, the catheters will be placed inside tumor tissue. Before the start of the series of hyperthermia treatments, the hyperthermia physician will determine whether it is possible to place a catheter directly into the tumor tissue. Placement of the catheter depends on the location of the tumor. It is not always necessary to have the sensor inside the tumor. Your physician will tell you if you need to have a temperature sensor inserted directly into the tumor. If you don't have a sensor inside the tumor, you will have a sensor inserted into the vagina. These sensors are used to monitor the heating.

The catheter placement will be done under local anesthesia if a catheter is placed inside the tumor tissue. This procedure may be painful for a moment as the local anesthetic is injected, but the pain should subside quickly after the catheter is inserted. You may be given antibiotics prior to the catheter insertion to prevent infection. The catheters are usually removed after the hyperthermia treatment is completed. Thus, repeat catheter placement is sometimes necessary.

Catheters can be removed quickly and painlessly if they cause discomfort. If a catheter is removed during treatment, another catheter will not be placed in that location and the hyperthermia treatment will continue. At a later hyperthermia session, your physician may decide to use a different catheter placement.

During treatment, a catheter may also be placed under your tongue every 30 minutes to monitor the temperature of your body.

CT Scans

Your physician will probably use a CT scan to determine if a catheter can be used to place temperature sensors directly in the tumor. If placing a catheter in the tumor is not possible, measurements will be taken to make sure the other temperature sensors are correctly placed on the skin and in body openings.

If your doctor determines that a temperature sensor can be placed in the tumor, another CT scan may be required to help your physician place one or two small catheters in the tumor so that temperature sensors can be inserted under your skin in the region of the tumor.

How Do I Prepare for a BSD-2000 Treatment?

Hyperthermia treatments are usually given in the radiation oncology department on an out-patient basis. Thus, you will not need to stay in the hospital overnight. You are not required to fast for hyperthermia treatments, but should avoid eating a heavy meal prior to your treatments. You should continue taking your prescription drugs. You should also drink plenty of fluids, as the hyperthermia treatment may increase your chances for dehydration. You may be required to have an enema prior to treatment. You may also be given pain medication and/or an oral pill to help you relax and reduce anxiety prior to treatment or as prescribed by physician.

You should not drive yourself home after the hyperthermia treatment. It is highly recommended that you have someone else prepared to take you home.

What Else Can I Do To Make the Treatment Easier?

Hyperthermia therapy in addition to radiation treatment can make you very tired. Each hyperthermia treatment will take 1½ to 3 hours. The treatment is very tiring and demanding. Therefore, it is important that you rest, relax and avoid strenuous activity before and after the treatment.

What Happens To Me Just Before the BSD-2000 Treatment?

As explained above, hyperthermia treatments are conducted in a shielded room to avoid interference of the RF energy with other devices. The frequency of the RF energy itself is not harmful to patients, and therefore, no individual protective shielding is needed inside the room.

Prior to entering the treatment room, you will be asked to dress in a standard hospital gown. Before the treatment begins, a number of very small temperature sensors will be placed to constantly monitor the temperature of various places on or within the body (please refer to the section above, *What Procedures Will Be Needed Prior To Treatment?)*. The catheters with the temperature sensors are placed inside or on your

body. Depending on the location of the tumor, catheters with the temperature sensors may be placed inside the tumor, on the skin and/or in natural body orifices. If possible, natural body openings, like the bladder, rectum, and vagina, will be used for insertion of the catheters with temperature sensors. A Foley catheter may also be placed in the bladder. Please discuss with your physician the procedures for placing a Foley catheter, and the risks involved with the placement.

Once you have had the catheters with temperature sensors placed and you are inside the treatment room, you will be helped onto a patient-support hammock. The doctor or technician will help you get comfortable. The clear plastic cylindrical applicator is then slid into place over the tumor area. Your head always remains outside of the applicator. You will be connected to various medical devices for monitoring your vital signs, including blood pressure, pulse, and core temperature. At this time, a water bolus inside the cylindrical applicator will be filled with water to form a tight seal against your skin. The water bolus is a plastic bag placed between the applicator and the target tissue. This bag, when filled with water, helps to regulate your skin temperature and direct the RF energy to the tumor.

If needed, some patients may be given medication to reduce anxiety. However, you will be awake during this procedure, as it is important for you to be able to provide verbal feedback to the operator.

What Will I Feel During the BSD-2000 Treatment?

After all the preparations are completed, your physician will begin the treatment. The BSD-2000 equipment will be operated from a room right next door to the treatment room. During the entire treatment you can talk to the people treating you via a window. Someone will regularly come into the treatment room to ask how you are doing and whether you need anything. You can drink water or have ice chips during treatment, if you wish.

When the treatment starts, you will be able to feel the heat inside the tumor. You will become warmer and may start to sweat. As you become warm, blankets/coverings can be removed, and the air conditioner and fans can be used to lower the temperature in the room. Cool, damp cloths can also be applied to your face. Your core body temperature may rise to about 38 °C (100.4 °F). The area where the tumor is located will be heated to a higher temperature. During the hyperthermia treatment the tissue is heated to a temperature between 40 and 45 °C (104-113 °F). Each treatment, including set-up time, lasts about 60-90 minutes.

The treatment should not be painful, but the treated area should be warm. Good tumor heating is a key to a successful treatment. The treatment may be uncomfortable at times, but it should never be painful. Tell your care team if you become too warm, especially if it occurs in a place that does not have a temperature sensor. You are the best thermometer. Notify the physician if you notice burning, pressure or otherwise

uncomfortable sensations. The technologist will adjust the equipment until the sensation subsides. Also, notify the physician if you notice that the water bolus is causing an intolerable amount of pressure.

The physician and nurse or technologist will ask you regularly how you are doing. Be honest with the physician regarding your pain or comfort level. The treatment can be stopped. Generally, minimal pain will be experienced in future sessions.

What Can I Expect After the BSD-2000 Treatment?

After the treatment is completed, you will start to cool down quickly. Someone will help you lift your head and feet so the support cushion can be placed under you to make it easier to get off of the hammock. After the hyperthermia treatment, it will take another 10 -15 minutes to remove the catheters.

You can shower at the hospital before you leave. The total duration of your stay in the hyperthermia unit will be approximately 1½ to 3 hours. You may feel tired for the remainder of the day. Be sure to drink plenty of fluids.

You should arrange for someone to bring you to your appointment and to take you home when your treatment is complete. You should not drive.

You may be given an antibiotic to prevent infection following your treatment.

What Are the Risks of a BSD-2000 Hyperthermia Treatment?

The hyperthermia physician will screen you to make certain you are a good candidate for hyperthermia. A serious heart condition, a pacemaker, prior radiation therapy to the treatment site, serious lung disease (like emphysema or COPD), significant neuropathy, or even artificial hips are reasons to rule out hyperthermia. The side effects that occur in radiation therapy are usually not worsened by the hyperthermia treatment.

Pain and Discomfort
You may experience a sensation of burning or pressure or otherwise uncomfortable sensations during the treatment. You may also experience pain during treatment. The percentage of patients who have reported some level of pain during hyperthermia treatments varies from 0 to 60%. The pain was frequently described as a burning sensation that usually stopped after adjustments were made. It is important that you tell your physician or nurse about any pain or discomfort during treatment so that they can make adjustments to reduce your pain and discomfort.

Fatigue
Prolonged duration of hyperthermia treatment combined with radiation therapy can cause fatigue. You may require more sleep and rest than usual during hyperthermia treatment.

Change in Bowel
You may experience a change in bowel activity, including diarrhea, loose stool, or frequency of bowel movements.

Burns
Skin problems can occur during hyperthermia. As a result of prolonged exposure to high temperatures during a treatment, some patients can develop a burn. These burns almost never develop on the skin (such as a blister). In about 10% of patients, a burn will develop in deeper seated tissue. A sub-dermal (under the skin) burn may form a lump that can be tender for one or more days. The lump will disappear on its own. A few patients have experienced small areas of muscle or fat necrosis (tissue death) due to damage to some healthy tissue caused by the hyperthermia. It is important that you tell your physician or nurse about any areas that feel particularly hot during treatment. If you develop a burn, it may require additional treatment, a reduction in power during hyperthermia treatment, or treatment may be stopped.

Painful Urination
Insertion of a catheter into the bladder may cause burning with urination for a few days. If the burning doesn't subside or worsens, please consult your physician to determine the cause of the irritation. If the burning persists, the catheter may be removed.

Infection
It's possible that, if you have temperature sensor catheters placed directly into the tumor tissue, the catheters may cause you discomfort or result in an infection. This side effect occurred in less than 1% of the patients studied. It is possible that the catheters may be left in place between hyperthermia treatments. If the catheters are left in place between treatments, you will be given instructions for caring for the catheters. The catheters may also be removed after the first or second treatment. Notify your health care provider immediately if you experience inflammation, increased pain or unexplained fever. Also, consult your doctor if your ability to sit is impaired or if you can feel the catheter in your sleep. Any of these conditions could lead to a decision to remove the catheter(s).

Two patients experienced extensive necrosis (tissue death) in the pelvic area and died two and three years following treatment with combined radiotherapy and hyperthermia using the BSD-2000 for cervical carcinoma treatment, a severe adverse event not reported in any other patients who have received hyperthermia and radiotherapy. The contribution, if any, of hyperthermia to this severe side effect, though unlikely, could not be completely eliminated.

Consult your physician immediately if you develop other problems that may be related to your hyperthermia treatments. Health care providers will be able to assess how to best treat your problem.

Listed below are possible side effects of hyperthermia treatment. However, these side effects were NOT experienced during the clinical study of the BSD-2000 system.

- Damage to non-target organs, possibly including fistula (an abnormal urine passage between the urethra and rectum).
- Temporary sterility (the therapy's effect on fertility is unknown).
- Worsening of pre-existing disease. Patients having borderline cardiopulmonary function secondary to coronary atherosclerosis, emphysema, or other conditions, may not be able to tolerate the additional systematic stress of extensive or prolonged hyperthermia.
- Increased drug activity. Elevated temperatures may be expected to affect the effect of some drugs.
- Thermal stress. Significantly increasing the core temperature of the body may result in thermal stress, *i.e.*, increased heart rate, blood pressure, and tachycardia.

In clinical studies on the BSD-2000 treatment system, most patients did not experience side effects. The majority of the side effects were reported within days after the treatment and disappeared shortly thereafter without any treatment. If at any time you are concerned about any side effect you may be experiencing, do not hesitate to contact your doctor.

When to Contact Your Doctor Immediately

- You see large amounts of blood (a spoonful or more) in your urine
- You see blood that is bright red in color
- There is leaking around the catheter
- You have a temperature above 101 °F
- You experience chills or shaking

More information

We hope that this brochure answered your questions about hyperthermia. If you have further questions regarding the treatment, consult your hyperthermia physician or technician.

Glossary of Terms

The following terms are used in this patient information brochure.

Antenna: A wire used to emit high frequency electrical energy.

Bolus: A plastic bag placed between the applicator and target tissue to help prevent burning and to confine and direct energy input.

Catheter: Small plastic tube inserted into or on the body that is used to hold the temperature sensors.

CT Scan: CT (computed tomography) scan is a medical imaging method used to generate a three-dimensional image of the inside of the body.

Hyperthermia: A method used to treat cancers within the body. External applicators are positioned around the body and radiofrequency energy is focused on the tumor to raise its temperature.

Disseminated Intravascular Coagulation: A blood clotting disorder.

Foley Catheter: Thin, sterile tube inserted into your bladder to drain urine.

General Anesthesia: Complete loss of feeling and consciousness, affecting the entire body following the administration of a drug or a gas.

Applicator: An antenna that transmits power to produce heat in tissue.

Hyperthermia Antenna: A metallic wire used for radiating radiofrequency and producing heat for hyperthermia treatments. These antennae are placed into catheters that have been implanted directly into the tumor.

Hyperthermia Equipment: The instruments used to deliver the heat treatment: a computer, generator, applicator and thermometry.

Hyperthermia Treatment: Heat delivered to the tumor area for a certain amount of time (usually 60 minutes) and to a therapeutic temperature (usually 40-42°C or 104 -107.5° Fahrenheit).

Ischemia: A condition in which blood flow (and thus oxygen) is restricted to a part of the body.

Local Anesthesia: Loss of feeling affecting a local area after the administration of a drug (usually xylocaine).

Local Infection: Body part invaded by bacteria that produces inflammation. The usual signs of infection are: pain, heat, redness and swelling-this can occur at the site of catheter insertion.

Necrosis: Death of tissue.

Neuropathy: Condition that results when nerves are diseased or damaged. Neuropathy can cause numbness, tingling, unusual sensations, and pain and can impair muscle movement.

Patient Support Hammock: A sling on which the patient lies during treatment.

Radiofrequency: An electromagnetic wave used especially in radio and television transmission; however, these waves are also capable of producing heat for therapeutic uses (hyperthermia).

Radiation Sensitizer: An agent or treatment that increases the effect of radiation.

Radiation Therapy: Medical treatments using x-rays or radioactive materials to kill cancerous or diseased tissues.

Reflected Power: Energy which is transmitted from an applicator and returned back to its source.

Stray Field: The region of energy transmitted from an applicator into the surrounding air rather than into the target tissue.

Temperature Sensors: Sensors enclosed in very small, plastic wires that are placed inside catheters, which then record the temperatures in the tumor or on the skin.

Vasoconstrictive: Any agent that causes a narrowing of a blood vessel.