The Effect of High Intensity Ultrasonic Irradiation on Tumor Growth

STEPHEN A. GOSS, MEMBER, IEEE, AND FRANCIS J. FRY, FELLOW, IEEE

Abstract—**High-intensity ultrasonic irradiation of the subdermally implanted Yoshida sarcoma was performed. Tumor placement was such that the lesion could be pulled away from the trunk section for complete and convenient irradiation. A focused ultrasonic irradiating system, consisting of a 5.5-cm diameter 4-MHz quartz transducer driven at resonance, was employed to provide a sound beam small enough in extent to effectively irradiate the tumor without seriously affecting overlying tissues. The therapeutic treatment involved movement of an intense continuous wave (1600 W/cm^2 *spatial peak, 4-second duration*) sound beam over the extent of the tumor volume in a matrix fashion, since the beam cross section was smaller than the tumor to be irradiated. Of 37 animals treated, about 35 percent presented nonpalpable tumors up to 120 days postirradiation. Among the remaining animals, tumor volume was reduced by about 85 percent over those of shams (significance at $p < 0.001$). The results demonstrate that a dramatic reduction in tumor growth can be affected by such therapy.**

I. INTRODUCTION

THE USE of ultrasound for cancer therapy has been under investigation for many years [1], with most recent emphasis placed upon the ultrasonic induction of hyperthermia. Focused ultrasound at intensity levels generally much greater than those used for hyperthermia may also be employed in cancer therapy to produce selective, irreversible tissue destruction. However, high intensity ultrasonic irradiation for cancer therapy has received relatively little attention.

Most of the work concerning the biological effects of high intensity ultrasound has largely dealt with biophysical studies where, for example, the identification of thresholds for irreversible damage [2], [3] or investigations of potential surgical applications [4]-[8] in relatively normal tissues have been considered. Nevertheless, a few studies have examined the effect of high intensity ultrasonic irradiation on tumor growth. Burov and Andreevskaya [9] applied high intensity (350 W/cm^2 CW) ultrasonic therapy to the treatment of the Brown-Pierce rabbit tumor transplanted to the testes, and reported elimination of not only the treated tumor, but also of nonirradiated metastatic nodules as well. Mishima [11] examined the effect of intense focused ultrasound (944 kHz, 100-1000 W/cm^2, 1-2 second exposure) on implantable gliomas induced with 20-methylcholanthrene. Tumors implanted in the abdominal wall were irradiated at 3 weeks postimplantation, and in the brain at 10 days postimplantation. The growth of abdominal tumors was suppressed at ultrasonic irradiations of 1000 W/cm^2 for 2 seconds, while 100 W/cm^2 at a 10-second treatment proved ineffective in suppressing growth. Kaketa and Wagai [12] examined the influence of high intensity ultrasonic (1 MHz) irradiation (5 seconds; 1 kW/cm^2) on the growth of Horie's sarcoma transplanted in the marrow of the femur of the rat, and of a sarcoma transplanted in the femur of the mouse. Significant reduction in tumor size over those untreated was observed six weeks after irradiation. The average survival period observed in 25 irradiated animals was 99.4 days, compared to 46.3 days for the 25 animals which constituted the untreated group. Similar results were reported in a subcutaneous Horie's tumor transplant in the rat, where the average survival of the animals increased from 56.3 to 81.1 days with the high intensity ultrasound treatment. Kishi *et al.* [13] irradiated a chemically derived glioma transplanted to the abdominal walls, with high intensity ultrasound three weeks after implantation, when the tumor was about 1 cm^3 in size. The tumors were irradiated for 6-30 seconds in nearly all regions with 944 kHz ultrasound at intensities up to about 1 kW/cm^2. Tumor masses irradiated with an intensity of at least 1 kW/cm^2 were observed to diminish in size, and animals receiving such treatment exhibited a significant prolongation in life-span over controls. For example, the mean survival time of 30 control animals was reported to be 74.6 days, while among 30 animals irradiated with ultrasound at 1000 W/cm^2 for 3 seconds, the average survival was reported to be 96.7 days. Also, grafts (small blocks of transplantable glioma) treated with similar ultrasonic doses were observed to exhibit significantly higher rejection rates after implantation in the abdominal walls of mice. Fry and Johnson [14] irradiated solid tumors produced via inoculation of the hamster flank with hamster medulloblastoma cells. Tumors were irradiated at a continuous wave (CW) frequency of 907 kHz and an intensity of 1000 W/cm^2 for 7 seconds, with a small ultrasound beam moved throughout the lateral extent of the tumor in 2-mm horizontal and vertical increments until the entire tumor was treated. In order to avoid severe skin burns resulting from the particular beam configuration employed, Fry and Johnson found it necessary to surgically expose the tumor for treatment, a procedure which is clearly unacceptable for clinical application. Nevertheless mean survival of the animals treated was significantly higher than shams, and about 30 percent of the ultrasound irradiated group exhibited complete tumor extinction.

In the present work, a focused irradiation system operating at 4 MHz is employed for intense ultrasonic treatment of subcutaneous solid tumors *in vivo* without prior surgical ex-

Manuscript received December 21, 1983; revised June 12, 1984. This work was supported in part by the Showalter Residuary Trust and in part by the Indianapolis Center for Advanced Research, Inc.

S. A. Goss is with URI Therm-X, Inc., 701 Devonshire Drive, Champaign, IL 61820.

F. J. Fry is with the Indianapolis Center for Advanced Research, Inc. 611 North Capitol Avenue, Indianapolis, IN 46204.

0018-9537/84/0900-0491$01.00

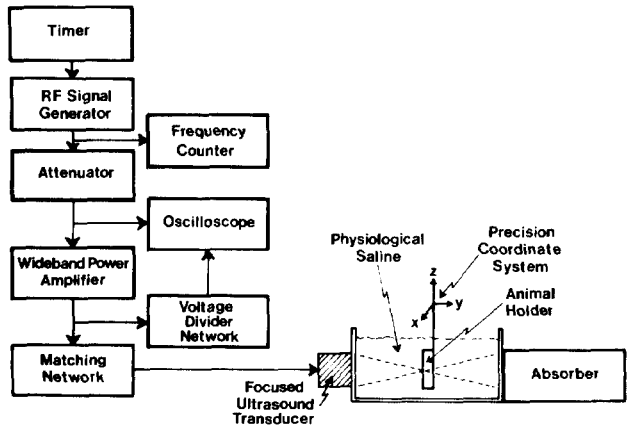

Fig. 1. Irradiation system employed in the intense ultrasonic treatment of subcutaneous solid tumors.

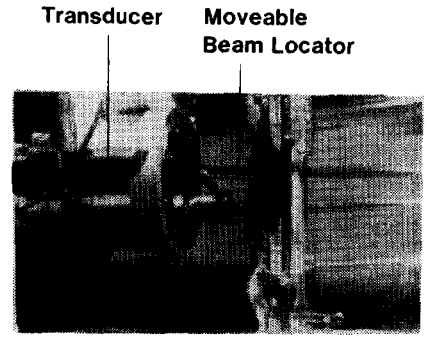

Fig. 2. Animal tumor being positioned for ultrasonic irradiation. Movable pointer is used to locate the focal region of the transducer relative to the tumor to be treated.

posure. This acoustic beam configuration allows effective irradiation of the tumor without seriously affecting overlying skin surfaces.

II. Methods

The ultrasonic irradiation system employed in these experiments, shown in Fig. 1, consists of a 5.5-cm diameter, 4-MHz focused quartz transducer driven at resonance by a 1-kW Instruments for Industry Model 469 wide-band amplifier. The longitudinal and lateral 3 dB beam widths of the transducer are 8.4 and 0.75 mm, respectively. A standard radio-frequency (RF) signal generator, controlled by a timer, and whose output is monitored by a frequency counter and oscilloscope, provides the amplifier drive signal. As the focal beam cross section of the transducer was small compared to that of the tumor, the animal was moved incrementally in the plane orthogonal to the longitudinal axis of the transducer by a precision coordinate system. The tumor was positioned such that it was irradiated in prescribed lateral and vertical increments until the entire tumor was treated. The longitudinal beam dimension was sufficient to effectively irradiate the entire depth of the tumor, when the longitudinal beam center corresponded to the central longitudinal region of the tumor.

Ultrasonic intensity determinations were made by the steel ball radiometer method [15]. For the present experiments, spatial peak ultrasonic intensities of 708 and 1600 W/cm^2, CW, were employed for a duration of 2-4 seconds per irradiation point. Irradiations were performed at intervals of about 10-20 seconds to ensure that excessive heating of the transducer lens system did not occur.

The tumor model employed in this experiment, provided by Eli Lilly & Company, Indianapolis, IN, was the Yoshida sarcoma implanted in the rat. The history and description of the Yoshida sarcoma may be found elsewhere [16]-[18]. The tumor was implanted by 0.5 cm^3 subdermal inoculation in the left flank of female Holtzman rats weighing about 160-200 grams. The tumor implanted in this manner is rapidly growing, and is generally fatal to the animal in 30-40 days. At Day 2 postinoculation the tumor size is about 0.8 × 1 × 1.3 cm deep, and is implanted in such a way that the lesion may be pulled away, from the trunk section of the rat, with the skin for more convenient and complete irradiation while avoiding the rib cage. Such tumor retraction was not severe, and is not considered to significantly alter the blood supply to the tumor. During the irradiation process, the anesthetized (ether followed by Metofane inhalation) rat is restrained in an apparatus designed to allow unimpeded beam approach, and is partially immersed in an acoustic coupling medium consisting of degassed physiological saline at 37°C. Prior to the placement of the animal in the restraint apparatus, the region around the tumor is shaved and depilated to permit better acoustic coupling. Fig. 2 shows an animal being positioned for irradiation, where a movable pointer locating the transducer focal position is aligned with the tumor. The demarcation of the tumor boundary was accomplished by transillumination and palpation of the extended flank region.

The experimental protocol for determining the effect of high-intensity ultrasound irradiation on tumor growth consisted of random separation of sham and ultrasound irradiated animals on the day the animals were inoculated, i.e., Day 0 of the protocol, for subsequent ultrasound or sham treatment on Day 2. Here, shams were treated the same as irradiated animals, including the animal restraint and tumor retraction protocols, with the exception that sound exposure did not occur. Successful tumor implantation was always evident on Day 2 for all animals in both the sham and irradiated groups. After treatment, tumor growth was followed for 28 days postinoculation. Tumor volume was calculated from external caliper measurements, assuming that the tumor took the form of an ellipsoid of revolution, at 8 intervals during the 28-day period. The total body weight of the animal was also monitored to assess qualitatively overall health. Sham animals and ultrasound irradiated animals in which tumors were palpated on Day 28 postinoculation were then sacrificed, photographed, and grossly autopsied for metastases. The autopsy consisted of an examination for palpable subdermal metastatic lesions, as well as a macroscopic search for such lesions in the thoracic and abdominal cavities and in major organs, including the liver, kidney, intestines, gall bladder, urinary bladder, rectum, colon, lung, and heart. The tumor was then surgically excised and measured. Ultrasound irradiated animals without palpable tumors on Day 28 postinoculation were followed to Day 120, when they too were sacrificed, photographed, and examined for proliferation of metastases.

TABLE I
ULTRASOUND EXPOSURE CONDITIONS

Irradiation Regime	Frequency (MHz)	Peak Intensity (W/cm^2)	Exposure Time (Sec)	Beam Spacing Lat. X Vert. (mm)
1	4	708	2	1 X 1
2	4	1600	4	0.5 X 1
3*	4	1600	4	0.5 X 1

*Area of irradiation extended 2 mm beyond periphery of the tumor.

The specific ultrasound exposure conditions employed in the present study are shown in Table I, where the peak intensity refers to the free-field spatial peak ultrasonic power per unit area in the focal plane, and the beam spacing refers to the lateral and vertical beam placement increment employed during the irradiation period. For example, in the single treatment session to which the animals in the present study were subjected (on Day 2 postinoculation), a tumor measuring 1 cm laterally and 1.2 cm vertically would, under Regime 1 in Table I, receive about 120 individual ultrasonic exposures spaced by about 1 mm, and each lasting 2 seconds. Using such an irradiation matrix, the entire tumor is treated while tight control of beam placement is maintained.

For Regimes 1 and 2, treatment was confined within the discernible edges of the tumor (as defined by palpation and transillumination). In Regime 3, the area of irradiation was extended 2 mm beyond the periphery of the tumor in order to assure effective coverage of the mass.

III. RESULTS AND DISCUSSION

The effect of high-intensity ultrasonic irradiation on tumor growth is shown in Figs. 3-5 for treatment Regimes 1-3, respectively, where the average tumor volume (cm^3) is plotted as a function of time (days postinoculation). These data are also summarized in Table II. In each figure, the upper curve represents the growth progression of sham irradiated tumors, while the lower curve represents the growth of tumors receiving ultrasound. For Regime 1 (Fig. 3) a reduction in growth of about 30 percent is observed in ultrasound irradiated tumors compared to shams; however, the difference is only marginally significant statistically (Student-t) over the time period over which the tumor growth was monitored (summarized in Table II). A greater effect is shown under Regime 2, in which the ultrasound intensity and irradiation density were increased. Under these irradiation conditions, at Day 28 the mean tumor volume among irradiated animals is about 16 percent of the mean sham value, and the volume reduction is significant ($p < 0.001$) over the entire 28-day period over which these measurements were made.

The final irradiation regime reported here, Regime 3 (Fig. 5), extended the same ultrasound intensity, exposure time, and beam placement spacing of Regime 2 to include an additional 2 mm of tissue about the periphery of the tumor as defined by palpation and transillumination. This protocol was employed in an attempt to irradiate viable tumor cells which may have escaped irradiation under Regime 2. The results of the administration of Regime 3, shown in Fig. 5, are similar to those

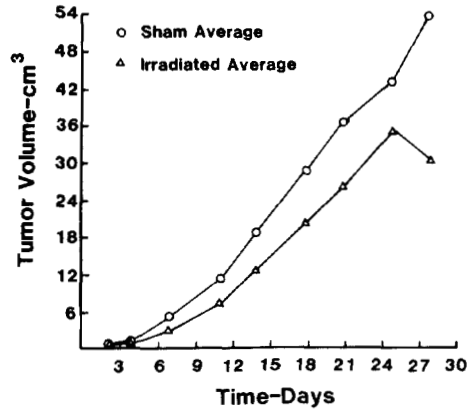

Fig. 3. Mean tumor volume as a function of the postinoculation time; Regime 1 exposure–Table I.

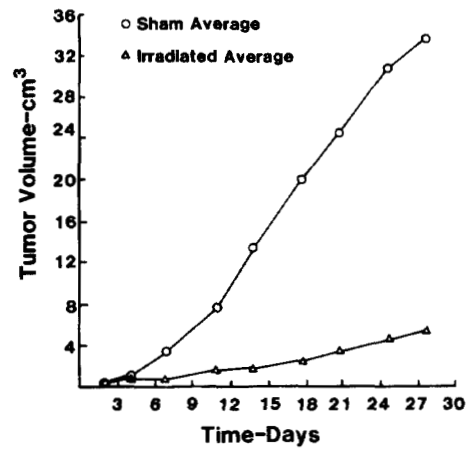

Fig. 4. Mean tumor volume as a function of the postinoculation time; Regime 2 exposure–Table I.

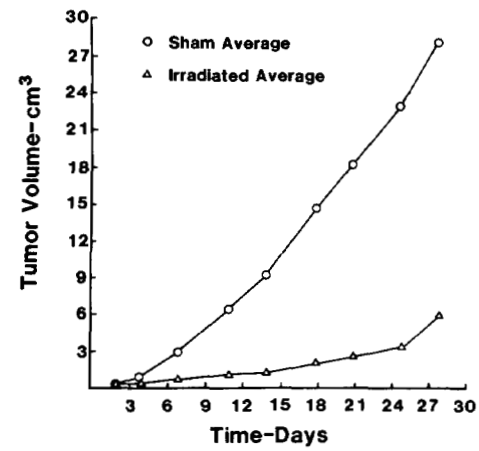

Fig. 5. Mean tumor volume as a function of the postinoculation time; Regime 3 exposure–Table I.

observed in Regime 2 (Fig. 4), with significant reduction of tumor growth over the entire 28-day period. It appears that little benefit is gained from irradiation of the tumor periphery. The mean volume of ultrasound irradiated tumors is 21 percent of that for shams 28 days postinoculation, similar to that obtained previously under Regime 2.

TABLE II
EFFECT OF ULTRASOUND IRRADIATION ON TUMOR GROWTH DATA SUMMARY

Regime	Days Postinoculation	Mean Sham Volume ± Std. Dev. (cm^3)	# Animals	Mean Irrad. Volume ± Std. Dev. (cm^3)	# Animals	Significance* (p)
1	7	5.21 ± 1.97	11	2.92 ± 0.96	11	<0.01
	14	19.0 ± 9.46	10	12.9 ± 7.06	11	NS
	21	37.0 ± 19.2	10	26.4 ± 18.7	10	NS
	28	54.3 ± 25.2	8	30.8 ± 9.23	8	<0.05
2	7	3.46 ± 1.10	23	0.751 ± 0.699	23	<0.001
	14	13.5 ± 5.53	23	1.85 ± 1.55	23	<0.001
	21	24.7 ± 12.6	21	3.54 ± 4.16	22	<0.001
	28	33.9 ± 16.5	18	5.5 ± 8.32	22	<0.001
3	7	3.00 ± 0.980	14	0.796 ± 0.881	16	<0.001
	14	9.29 ± 3.67	14	1.24 ± 1.06	16	<0.001
	21	18.4 ± 8.37	12	2.58 ± 3.01	14	<0.001
	28	28.3 ± 16.4	10	6.05 ± 7.87	12	<0.01

*$p > 0.1$ considered not significant (NS).

Since there is some variation in growth among the sham groups employed in the study, it is difficult to precisely compare the effect of the irradiation of Regimes 1-3 on tumor growth. The explanation for differences in tumor growth among the sham population is not clear, since the inoculation technique, as well as the tumor source from which the brei forming the inoculate was derived, was common to all groups. Of all of the animals inoculated for this study, 100 percent presented palpable masses two days postinoculation. In any case, each irradiation regime examined employed matched sham groups, such that differences in sham tumor size between animals of the three irradiation regimes impact most importantly on the intercomparison of treatment protocols, and less upon the assessment of effectiveness of each independent treatment regime. Since both the intensity and exposure spacing differed between Regime 1, and Regimes 2 and 3, one cannot form a clear-cut dose response relationship from these data based upon a particular exposure variable irrespective of differences in tumor growth rate in the animal population. Nevertheless, one can identify gross trends in the comparative effectiveness of each exposure, under the constraints previously described, by presenting the data for each regime as the normalized difference between the mean sham volume and the mean irradiated volume, using the expression:

$$\Delta V(\%) = \frac{V_s - V_i}{V_s} \times 100\%. \quad (1)$$

Here, V_s and V_i are the mean sham and irradiated tumor volumes, respectively, and $\Delta V(\%)$ is the normalized difference in sham and irradiated tumor volume. These normalized data are plotted as a function of time postinoculation in Fig. 6. The use of Regime 1 resulted in an initial 30-40 percent volume reduction over shams which diminished with time. (The Day 28 data point is skewed by the loss of two sham and two irradiated animals just prior to Day 28 due to massive tumor growth.) Regimes 2 and 3, however, are seen to be nearly identical in effectiveness, with an overall volume reduction of about 85 percent which persists throughout the 26-day period following irradiation. Since the irradiation conditions of Regimes 2 and 3 were identical, with the exception of the extra-peripheral irradiation, the good agreement in therapeutic response between Regimes 2 and 3 observed in Fig. 6 suggests a degree of repeatability among the groups of animals employed in this study.

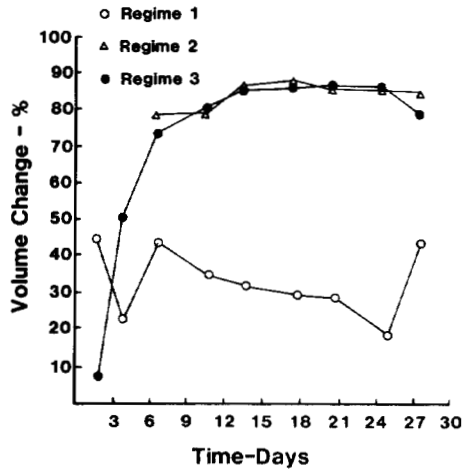

Fig. 6. Normalized volume differences between sham and irradiated tumors using irradiation Regimes 1-3.

A number of irradiated animals exhibited tumors which could not be palpated at Day 28 postinoculation. These animals were not sacrificed on Day 28, but were monitored up to 120 days postinoculation, when the tumor volume measurements and gross autopsies were performed. No evidence of the primary tumor was found in these animals, nor of metastases. A summary of these data is shown in Table III where it is seen that the animals exhibiting nonpalpable tumors were confined to those which received ultrasonic irradiation Regimes 2 and 3. No sham animal under any regime, or irradiated animal under Regime 1, exhibited complete tumor regression. Among animals irradiated under Regimes 2 and 3, however, 30-35 percent of the animals exhibited nonpalpable tumors at Day 28, with complete tumor regression confirmed at 120 days postinoculation.

Another result of the study concerns the development of metastases among the various experimental groups, summarized in Table IV. While there appears to be a relatively small but

TABLE III
INCIDENCE OF COMPLETE TUMOR REGRESSION AMONG EXPERIMENTAL ANIMALS

Experimental Group	Animals Employed[1]	Nonpalpable[2]	Percent
All shams[3]	36	0	0
Regime 1 (irradiated)	8	0	0
Regime 2 (irradiated)	22	8	36.4
Regime 3 (irradiated)	12	4	33.3

[1] Surviving at Day 28 postinoculation.
[2] No evidence of tumor presence up to 120 days postinoculation.
[3] Combined shams from Regimes 1-3.

TABLE IV
FRACTION OF ANIMALS EXHIBITING METASTASES

Irradiation Regime	Total Shams[1]	Shams with Metastases	Percent	Total Irradiated[1]	Irradiated with Metastases	Percent
1	11	1	9	11	1	9
2	23	10	43.5	23	6	26
3	14	6	42.8	16	4	25

[1] At Day 2 postinoculation.

equal incidence of irradiated and sham animals with metastases associated with experimental Regime 1, the fraction of irradiated animals in experimental Regimes 2 and 3 exhibiting metastases were about 60 percent of the fraction of shams in which metastases were observed. This effect could be associated with the dramatic reduction in primary tumor growth produced by irradiation Regimes 2 and 3, or possibly with some form of systemic response of the animal brought about by the massive amount of tumor destruction produced by the high-intensity ultrasonic irradiation over a relatively short span of time.

Another interesting observation concerns the growth progression of sham and irradiated tumors over the course of the experiment. Fig. 7 shows a log-log plot of tumor volume versus time postinoculation, where it is evident that the sham irradiated group exhibits an essentially power volume growth with time from Day 2 to Day 28. The growth of irradiated tumors is somewhat different, however. When the growth data of tumors irradiated under Regimes 2 and 3 are separated according to whether a palpable mass could be detected at the point of original tumor implantation 28 days postinoculation (palpable and nonpalpable in Fig. 7), the growth progression of irradiated tumors which go to eventual extinction can be retrospectively compared to the growth of those which were palpable at the end of the observation period. Referring to Fig. 7, it is clear that up until about 6-8 days postinoculation, the average growth of both tumor groups (palpable and nonpalpable), under either irradiation regime, exhibits a similar pattern. After that time, however, the nonpalpable tumor groups under either irradiation regime digress in growth to extinction, with a "peak" in growth occurring 6-10 days postinoculation, while the remainder of tumors continue to grow at a rate comparable to those of the sham group. It is not clear what mechanism is responsible for this growth behavior. The growth rates of eventual palpable and nonpalpable masses

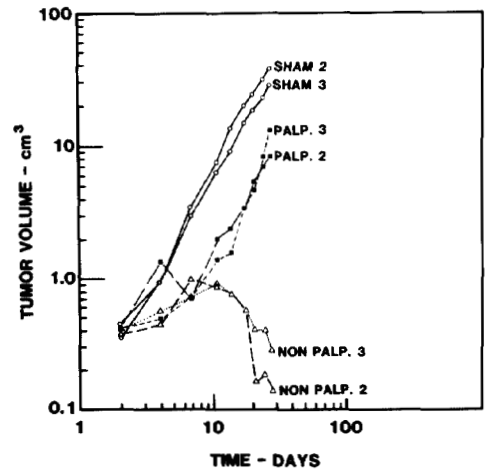

Fig. 7. Logarithmic plot of mean tumor volume as a function of time, for irradiation Regimes 2 and 3. Here, the growth of irradiated tumors which digressed to extinction are separated from those tumors still palpable in the animal on Day 28 postinoculation.

were similar for about one week postirradiation and were significantly less than those for the corresponding sham groups.

No attempt was made to measure temperature rise in the tumor mass in this study. From other studies involving tissue irradiation, it is apparent that the temperature rise is quite high [19]. The upper limit to temperature rise at 1600 W/cm^2, 4-second exposure duration, can be estimted by the following calculation, assuming temperature equilibrium will not be reached during the short exposure:

$$\Delta T = \frac{2\alpha I}{\rho C J}\,\Delta t \doteq \frac{2(0.03)\,(1600)}{4}\,(4) \doteq 96^{\circ}\mathrm{C}, \tag{2}$$

where ΔT is the temperature rise in °C, α is the pressure absorption coefficient in cm^{-1}, I is the acoustic intensity in W/cm^2, ρC is the heat capacity per unit volume in cal °C/cm^3,

J is the mechanical equivalent of heat in J/cal, and Δt is the irradiation time in seconds.

After cessation of exposure, the temperature drop is quite rapid, and we presume that in the 10-15 second interval between each irradiation the temperature has reached its normal value.

IV. Summary

The results of the high-intensity ultrasonic treatment of the Yoshida sarcoma complement the earlier studies in the medulloblastoma (HM) of the hamster [14], as well as with other earlier studies [11]-[13], and demonstrate that dramatic reduction of tumor growth can be effected by such treatment.

At a spatial peak intensity of 1600 W/cm^2 (4-second duration per exposure applied every 0.5 mm laterally and 1 mm vertically over the extent of the tumor), tumor volume of ultrasound irradiated animals was reduced to 85 percent of the volume found in shams. Complete tumor ablation, measured by the absence of a palpable mass 120 days postinoculation, was effected in 35 percent of the animals treated.

Acknowledgment

The authors gratefully acknowledge Eli Lilly & Company, and especially Dr. Gerald Grindey of that institution, for providing the tumor inoculated animals employed in this work. The authors also acknowledge the contributions of Ms. Anita Bush and Ms. Jennifer Shrote to the experimental phases of this work.

References

[1] F. W. Kremkau, "Cancer therapy with ultrasound: A historical review," *J. Clin. Ultrasound*, vol. 7, pp. 287-300, 1979.

[2] F. J. Fry, G. Kossoff, R. C. Eggleton, and F. Dunn, "Threshold ultrasonic dosages for structural changes in the mammalian brain," *J. Acoust. Soc. Amer.*, vol. 48, pp. 1413-1417, 1970.

[3] F. Dunn and F. J. Fry, "Ultrasonic threshold dosages for the mammalian central nervous system," *IEEE Trans. Biomed. Eng.*, vol. BME-18, pp. 253-256, 1971.

[4] F. J. Fry, "Intense focused ultrasound: Its production, effects, and utilization," in *Ultrasound: Its Applications in Medicine and Biology, Part II*, F. J. Fry, Ed. New York: Elsevier, ch. XIV, pp. 689-736.

[5] R. Meyers, W. J. Fry, F. J. Fry *et al.*, "Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders," *J. Neurosurgery*, vol. 16, pp. 32-54, 1959.

[6] W. J. Fry and R. Meyers, "Ultrasonic method of modifying brain structures," *Confin. Neurol.*, vol. 22, pp. 315-327, 1962.

[7] C. A. Linke, E. L. Carstensen, L. A. Frizzell, A. Elbadawi, and C. W. Fridd, "Localized tissue destruction by high intensity focused ultrasound," *Arch. Surg.*, vol. 107, pp. 887-891, 1973.

[8] F. L. Lizzi, D. J. Coleman, J. Driller, L. A. Franzen, and F. A. Jakobiec, "Experimental, ultrasonically induced lesions in the retina, choroid, and sclera," *Invest. Ophthal. Visual Sci.*, vol. 17, pp. 350-360, 1978.

[9] A. K. Burov and G. D. Andreevskaya, "Action of high intensity ultrasonic vibrations on malignant tumors of animals and man," *Doklady Akad. Nauk. S.S.S.R.*, vol. 106, pp. 445-448, 1956.

[10] A. K. Burov, "High intensity ultrasonic oscillations for treatment of malignant tumors in animals and man," *Doklady Akad. Nauk. S.S.S.R.*, vol. 106, pp. 239-241, 1956.

[11] T. Mishima, "Effects of intense focused ultrasound on implantable gliomas of mice," *J. Wakayama Med. Soc.*, vol. 26, pp. 149-166, 1975.

[12] K. Kaketa and T. Wagai, "Destruction of malignant tumor by intense focused ultrasound," in *Annual Report (1970) of the Medical Ultrasonics Research Center*, Juntendo University School of Medicine, Hongo, Tokyo, Japan, pp. 35-39, 1971.

[13] M. Kishi, T. Mishima, T. Itakura, K. Tsuda, and M. Oka, "Experimental studies of effects of intense ultrasound on implantable murine glioma," in *Proc. 2nd European Congress on Ultrasonics in Medicine*, Munich, May 12-16, 1975. (*Excerpta Medica*. Amsterdam-Oxford, 1975, pp. 28-33.)

[14] F. J. Fry and L. K. Johnson, "Tumor irradiation with intense ultrasound," *Ultrasound Med. Biol.*, vol. 4, pp. 337-341, 1978.

[15] F. Dunn and F. J. Fry, "Ultrasonic field measurement using the suspended ball radiometer and thermocouple probe," in *Interaction of Ultrasound and Biological Tissues*, DHEW Publ. No. (FDA) 73-8008; BRH/DBE 73-1. Washington, DC: U.S. Govt. Printing Office, 1972, pp. 173-176.

[16] T. Yoshida, Y. Muta, and Z. Sasaki, "Z. Studien uber das Ascites-Sarcoma," in *Proc. Imp. Acad. Tokyo*, vol. 20, pp. 611-616, 1944.

[17] H. L. Stewart, K. C. Snell, L. J. Dunham, and S. M. Schlyen, *Transplantable and Transmissible Tumors of Animals*. Washington, DC: Armed Forces Institute of Pathology, 1959.

[18] J. A. Dickson and M. Suzanger, "*In vitro-in vivo* studies on the susceptibility of the solid Yoshida sarcoma to drugs and hyperthermia (42°C)," *Cancer Res.*, vol. 34, pp. 1263-1274, 1974.

[19] P. P. Lele, "Thresholds and mechanisms of ultrasonic damage to 'organized' animal tissues," presented at the Symp. on Biological Effects and Characterizations of Ultrasound Sources, USDHEW, Public Health Service, Food and Drug Administration, Dec. 1977.

Stephen A. Goss (S'72-M'78) was born on November 21, 1949 in Chicago, IL. He received the B.S., M.S., and Ph.D. degrees in electrical engineering from the University of Illinois, Urbana, in 1972, 1974, and 1978, respectively.

From 1978 to 1983 he was a Research Scientist at the Indianapolis Center for Advanced Research, Inc., where he worked in ultrasound biophysics, dosimetry, and cancer therapy and in the medical diagnostic applications of ultrasound. He was also an Assistant Professor of Radiology at the Indiana University School of Medicine from 1982-1983. Since 1983 he has been associated with URI Therm-X, Inc., Champaign, IL, where he is presently engaged in the research and development of ultrasound hyperthermia delivery systems and associated instrumentation.

Dr. Goss is a member of the Acoustical Society of America, the American Institute of Ultrasound in Medicine, and Sigma Xi.

Francis J. Fry (M'41-SM'81-F'82) was born in Johnstown, PA, on April 2, 1920. He received the B.S. in electrical engineering from the Pennsylvania State University, University Park, in 1940, and the M.S. in electrical engineering from the University of Pittsburgh, Pittsburgh, PA, in 1946.

He has held various positions in both university and private industry throughout his career. He is presently an Adjunct Professor of Surgery at the Indiana University School of Medicine, Sonic Research Engineer at the Indianapolis Center for Advanced Research, Inc., and Vice President of Technology Development Corporation. Much of his career has been concerned with the interaction of ultrasound with biological tissue and ultrasonic medical instrumentation.

Mr. Fry is a Fellow the Acoustical Society of America and the American Institute of Ultrasound in Medicine.