Cadaveric Study for the Effects of Interstitial Thermotherapy

Bir Kadavra Çalışmasında İnterstisyel Termoterapi Etkisi

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Özet: Beynin merkezinde yer alan tümörler interstisyel düşük lazer enerjisi ile koagüle edilebilirler. Ancak salınan lazer enerjisi sadece tümör içerisinde değil aynı zamanda yakın nöral yapılarda da yerel ısı artışına yol açabilmektedir. Bu çalışmadaki amaçlarımızda denatüre edilecek beyin hacmi ile uygulanması gereken lazer enerjisi arasındaki ilişkiyi ve zaman içinde komşu nöral dokularda gelişebilecek sıcaklık artışlarını araştırmaktı. Bunun için dana kadavrası beyinlerine değişik çıkış güçlerinde, sürelerinde ve zaman dilimlerinde lazer uyguladık. Denatüre olan hacimler (çapları 1.5 ile 8 mm arasında değişmekteydi) ile beyin yüzeyi ısı yayılımları (termografik olarak 35.1°C'a karşılık gelen bölgelerin çapları 15 ile 30 mm arasında değişmekteydi) arasında belirgin bir farklılık mevcuttu. Yine 350 ile 3000 jül arasında lazer enerjisi uygulandığında lazer probunun ucuna 1 cm kadar uzak olan dokulardaki sıcaklık artışları 5.1 ile 16.1 C arasında değişmekteydi. Bu bulguların, klinikte interstisyel termoterapiye olan katkıları tartışılmıştır.

Anahtar Sözcükler: Lazerler, yerel hipertermi, sterotaksik termoterapi, Nd-YAG lazer-tümör denatürasyonu

Summary: *The central brain tumors can be coagulated with interstitial low laser energy. The delivered laser energy may however produce local hyperthermia not only in the tumor tissue but also in nearby neural structures. In this study, our goals were to investigate the relationship between denaturated brain volume and delivered joules of laser energy and also the temperature increases on adjacent neural tissues as a function of time. We subjected cadaveric calf brains to various output powers, intervals and durations of laser irradiation. There was a remarkable discrepancy between the denaturated volumes (diameters ranged between 1.5 and 8 mm) and brain surface heat distributions (diameters of thermographic areas corresponding to 35.1°C ranged between 15 and 30 mm). Also temperature increases in tissues as close as one centimeter away from the tip of the laser probe, ranged between 5.1 and 16.1°C with delivered laser energies from 350 to 3000 joules. Application of these findings to clinical interstitial thermotherapy is discussed.*

Key Words: *Lasers, local hyperthermia, stereotactic thermotherapy; Nd-YAG laser- tumor denaturation.*

Local hyperthermia is an accepted treatment for some malignant tumors (1,2). As a source of local hyperthermia, the Nd:YAG laser is used for stereotactic interstitial irradiation of cerebral tumors. The aim of the procedure is the denaturation of deeply situated, surgically inaccessible tumors with minimal damaging nearby neural structures (3). The advantage of lasers is the very precise delivery of energy to tissues and good instrumental control of total energy deposition (4). In our study, we investigated the temperature differences, heat distributions, and macroscopic sizes of lesions after various laser irradiation conditions during interstitial thermotherapy. Our aim was to search a correlation between these parameters, and have some clues for clinical application. We tried to compare denaturated brain volumes with delivered laser energy deposition, and to determine induced thermal changes in nearby structures.

Materials and Methods

In this invitro study, cadaveric calf brains were subjected to laser irradiation of various conditions to evaluate three different parameters related with local hyperthermia; temperature differences, brain surface heat distributions, and pathological changes. For investigating these parameters, 18 different laser irradiation conditions were used. Each condition was performed in 7 different samples. 126 specimens were used during the experiments.

We used a Neodymium-yttrium-aluminum-garnet (Nd: YAG) laser device (wavelength 1.064 Nm, Messerschmitt-Bolkow-Blohm-GmbH, Germany) with its bare fiber (outer diameter 1.0 mm). The tip of the laser probe was inserted in 1 cm deep into the cortex.

Laser irradiation was done under the following conditions:

a) Output powers were 5, 6, or 7 watts (W).

b) Pulse intervals at each power level were 0.3 or 0.6 seconds.

c) Total irradiation times were 5,10, or 15 minutes.

For each irradiation condition, length of pause between every pulse was 1 second.

The temperature changes were measured minute by minute with thermocouples placed 1 cm lateral to the tip of the laser probe. The temperatures of the brains before laser exposure were 20±2.0°C.

Heat distribution on the brain surface was observed with thermography plates placed over irradiated brain tissues. As soon as laser irradiation had finished, we measured the diameter of the innermost circle, corresponding to 35.1°C in order to make comparisons between various laser conditions. Then, the thermographic plate appearance was photographed immediately.

The specimens were thinly sectioned and their appearance were photographed after their diameters had been measured. Finally volumes of the lesions were calculated in order to make comparisons with different variables.

For the statistical analysis, data were collected in ten groups which were established according to applied joules of laser. Our four variables were applied joules of laser, temperature differences (recorded 1 cm a way from tip of laser probe), thermographic diameters (corresponding to 35.1°C), and macroscopic diameters of the induced lesions. Correlation between variables were examined with correlation and regression analysis, and the significence of correlation was checked with t-test. Comparisons between the groups were made with ANOVA. Since number of the samples in each group were not same, differences between the groups were controlled with the least significant difference test.

Results

Temperature increases: Temperatures in the cortex increased consistently with increasing laser power, interval and pulse duration (Table I). At 5 watts, the recorded increases in the temperatures varied between 5.1 and 13.0°C depending on the interval and duration. These variations were between 7.0 and 14.1°C, and 7.2 and 16.1°C for the output powers of 6 watts and 7 watts, respectively. In other words, applied joules of laser were closely related with temperature increases recorded one cm a way from the tip of the probe. But the ratios of increase in both joule temperature increase, were not equal. Mean temperature increases for 1000, 2000 and nearly 2900 joules of laser were about 10.2, 13.3, and 14.1°C, respectively. These findings were in accordance with our decision of making a comparison between duration of laser irradiation and temperature increase (Figure 1).

Thermographic diameters: The thermographic appearance of the heat distribution for each irradiation

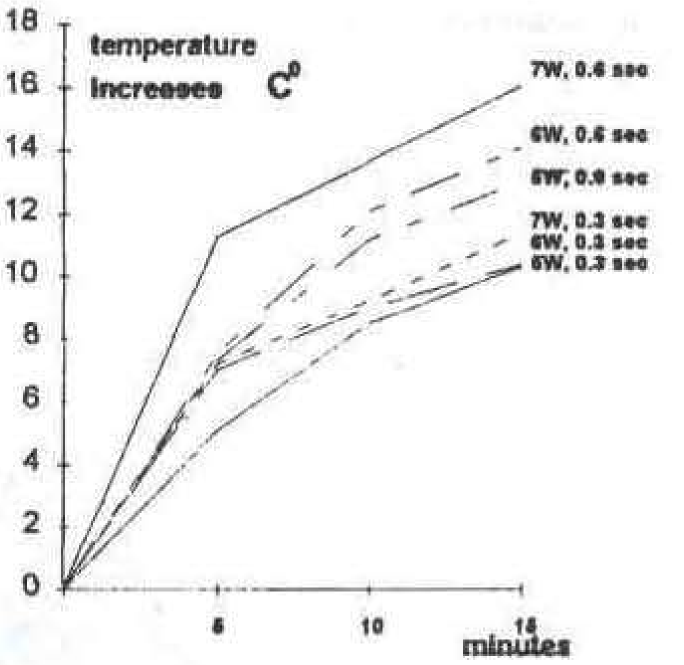

Figure 1. Time scale of temperature increases of calf brain undergoing laser irradiation of various conditions. Temperature increases were in accord with the increasing duration of each joule of laser.

condition was similar, ranging from round to ellipsoid shapes, and forming a concentric circle pattern during laser irradiation on the thermographic plate (Figure 2). The diameters of the inner circle of the thermographic figures (corresponding to 35.1°C) increased in proportion to the increase in laser output power, interval, and duration (Table I). At 5 watts, the diameters varied between 15 and 22 mm depending on intervals and durations. These values were between 17 and 26 mm and 19 and 30 mm after the output powers of 6 watts and 7 watts, respectively. Briefly, increase in thermographic diameters were in proportion to applied joules of laser. Mean thermographic diameters measured after 1000, 2000, and nearly 2900 joules were 21.3, 21.0, and 30 mm, respectively.

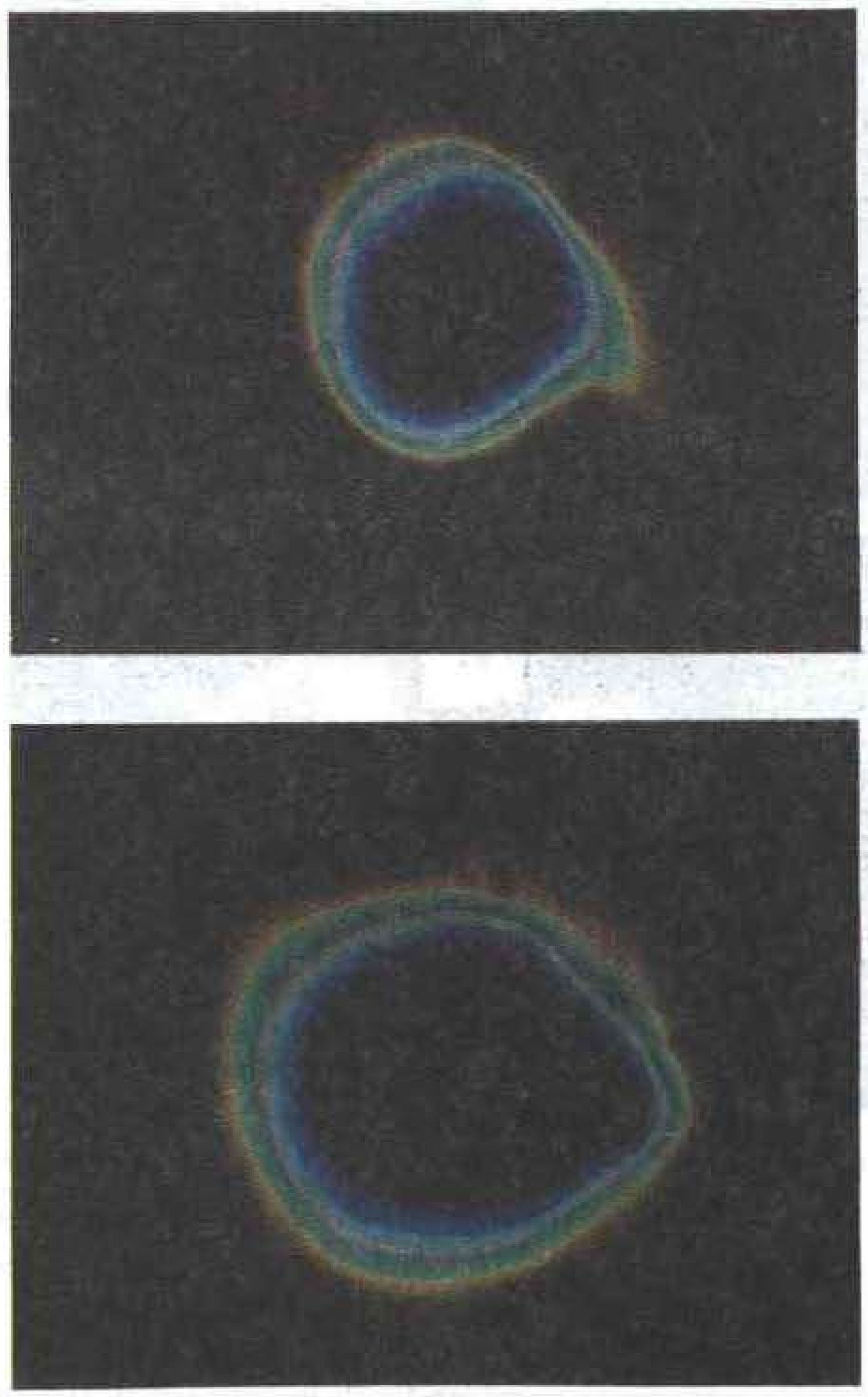

Figure 2. Thermographic appearance of heat distribution during ITT was forming an ellipsiod concentric pattern. (A) Diameters of the innermost circle were reaching 21 and 27 mm after 966 (A) and 2484 (B) joules of laser irradiation, respectively.

Table I. Mean temperature increases (Ti), brain surface thermogram (Td) corresponding to 35.1°C and irradiated cavitiy (Md) diameters after laser irradiation of pulse intervals, output powers and total duration.

INTERVAL	0.3 sec.									0.6 sec.								
POWER	5 watts			6 watts			7 watts			5 watts			6 watts			7 watts		
TIME	Ti	Td	Md	Ti	Td	Md	Ti	Td	Md	Ti	Td	Md	Ti	Td	Md	Ti	Td	Md
5 min.	5.1	15	1.5	7.0	17	2	7.2	19	2.5	7.3	17	3	7.5	18	4	11.3	21	4
10 min.	8.5	22	3	9.0	18	4	9.2	21	5	11.2	18	4	12.1	20	5	13.7	27	7
15 min.	10.3	22	4	10.4	22	4.5	11.4	21	6	13.0	21	6	14.1	27	7	16.1	30	8

Macroscopically, a spherical cavity surrounded by a carbonated layer of tissue was found around the tip of the laser probe (Figure 3). The size of the spherical voids created by the energy varied in proportion to the amount of laser energy delivered. The diameters of the voids varied between 1.5 and 6 mm after 5 watts of laser application. These values ranged between 3.0 and 7.0 mm, and 4.0 and 8.0 mm after 6 and 7 watt laser applications, respectively (Table I). Macroscopic diameters were also changing with applied joules. Mean diameters for 1000, 2000, and nearly 2900 joules were

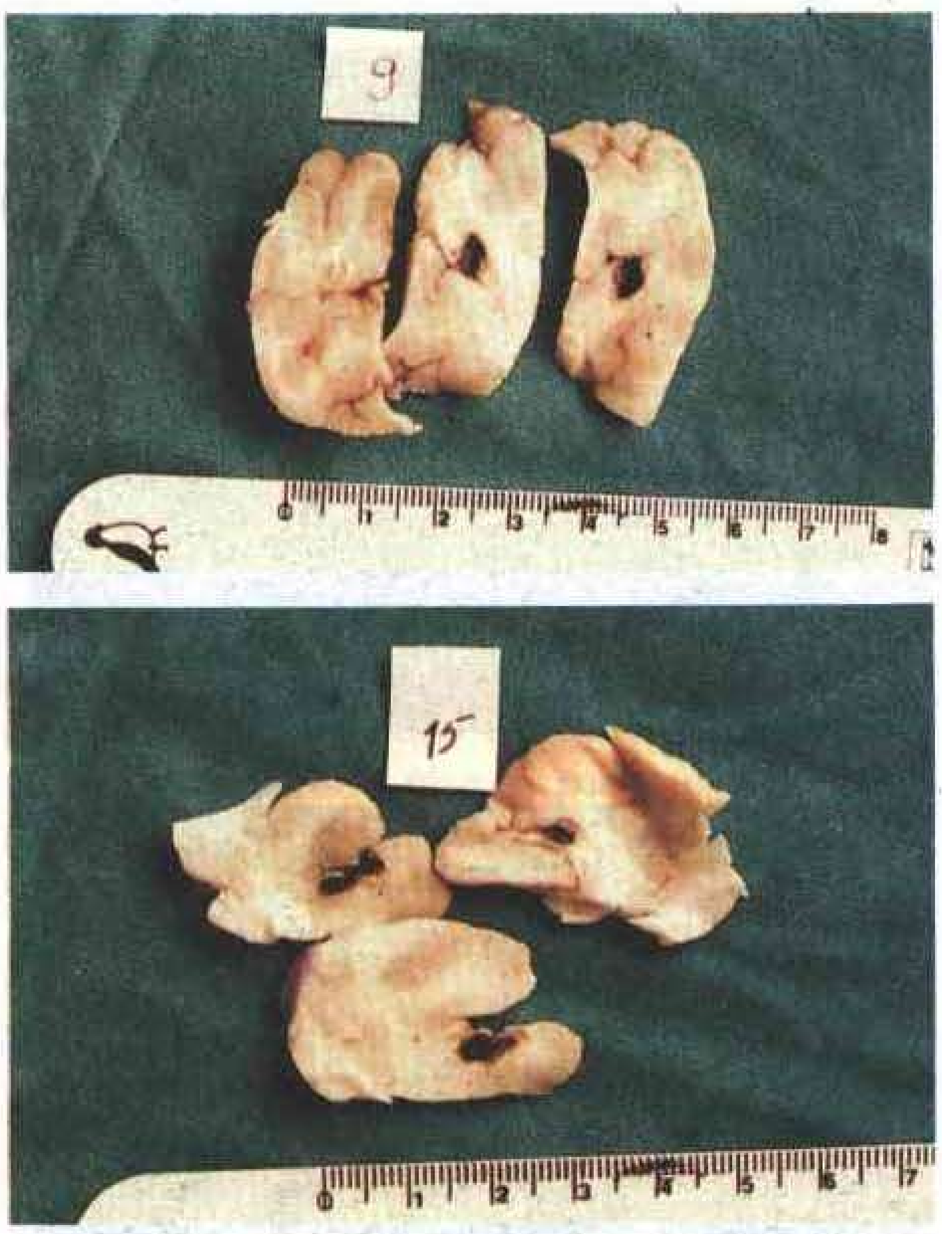

Figure 3. Macroscopic lesion induced during ITT were a spherical cavity surrounded by a carbonated layer of tissue. Diameters of lesion were 4 mm and 7 mm after 966 (A) and 2484 (B) joules of laser irradiation, respectively.

4.3, 6.2, and 8 mm, respectively. But, when the denaturated volumes were compared with joules, correlation of increases became more prominent. Thus, we have been able to construct a volumetric determination of laser energy deposition (Figure 4). We also compared the diameters of the innermost thermographic circles with the diameters of the laser-induced lesions on the specimens. Great discrepancy was observed between these two parameters (Figure 5).

Statistical analysis: Correlation analysis between the four variables, showed a positive correlation (Table II). All the correlation coefficients (r) were greater than 0.40096 [the critical value (1-tail,.05)] ($p<0.05$). t-test was performed for checking significance of correlation

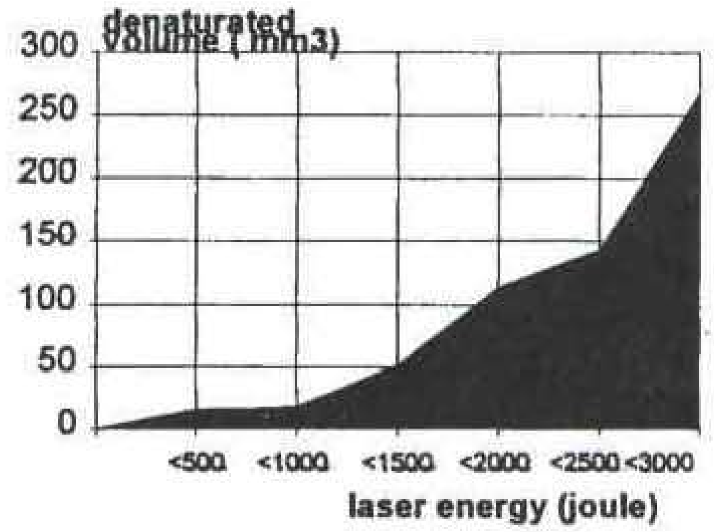

Figure 4. Volumetric relationship of denaturated cavities and delivered laser energy. Denaturated volume of the brain tissue was beginning to increase much more especially after applying 1000 joules of laser energy.

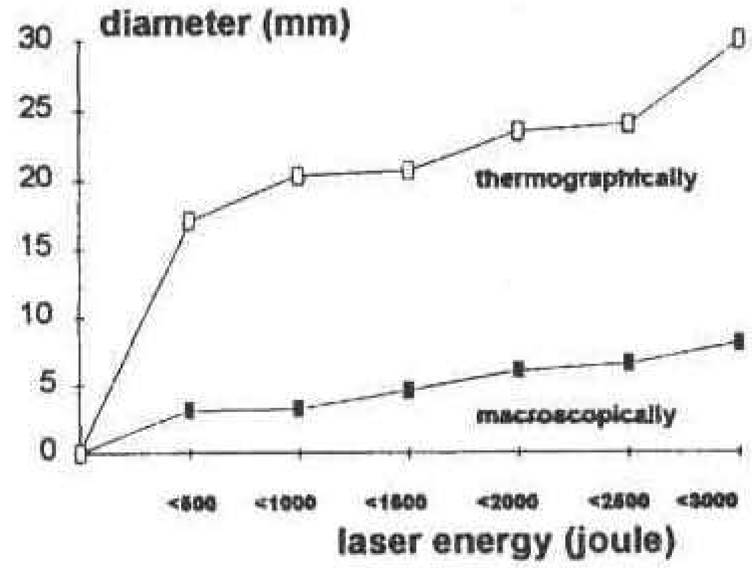

Figure 5. Diameters of brain surface thermograms (Td) and denaturated cavities (Md) after various irradiation conditions. It is apperant that in achieving a certain diameter of a tissue denaturation, several times of that diameter of tissue should be heated.

Table II. Mean values and standart deviations (SD) of each parameter are listed according to applied joules of laser. Correlation-regression analysis between all four variables revealed a positive linear correlation. Then, t-test showed the significence of all correlation coefficients, except joule-macroscopic diameter and thermographic-macroscopic correlations ($p<0.05$).

Groups	n=	Joules	Temperature Increases		Thermographic Diameters		Macroscopic Diameters	
			mean	SD	mean	SD	mean	SD
I	7	345	5.10 ±	0.21	15.00 ±	1.29	1.50 ±	0.40
II	14	414-483	7.10 ±	0.32	18.00 ±	1.79	2.25 ±	0.61
III	14	690	7.90 ±	0.67	19.50 ±	3.00	3.32 ±	0.77
IV	14	828	8.25 ±	0.85	18.00 ±	1.35	4.00 ±	0.55
V	21	966-1035	10.26 ±	0.94	21.33 ±	1.85	4.33 ±	0.78
VI	14	1242-1380	10.80 ±	0.62	20.00 ±	2.80	4.25 ±	0.61
VII	14	1449-1656	11.75 ±	0.54	20.50 ±	1.60	5.50 ±	0.91
VIII	14	1932-2070	13.90 ±	0.38	21.00 ±	1.73	6.28 ±	0.85
IX	7	2484	13.00 ±	0.38	27.00 ±	2.07	7.00 ±	0.75
X	7	2898	16.10 ±	0.47	30.00 ±	2.16	8.00 ±	0.86

* The least significant difference test revealed no significant differences between groups II and III for temperature increases, II to IV, and II to VIII for thermographic diameters, and IV to VI for macroscopic diameters ($p<0.05$).

coefficients. Although regression analysis showed a linear correlation between all variables, t-test revealed no significance for coefficients of joule-macroscopic diameter, and termographic-macroscopic diameter correlations. No significant difference of temperature increases were induced between the irradiation conditions, ranging from 414 to 690 joules. When we compared thermographic diameters, we have not found significant differences between groups II to IV (414 to 828 joules), and III to VIII (690 to 2070 joules). Macroscopic diameters were differing significantly in each group, except in groups IV to VI (828 to 1380 joules).

Discussion

As a treatment modality, lasers may be used for inducing hyperthermia in malignant tissue (5). Brain tumors invading central, surgically inaccessible structures are prime targets for interstitial thermotherapy (ITT) which is the stereotactic destruction of the tumor tissue (3). The high energy induces an ellipsoid coagulation necrosis surrounded by an edematous area (6,7). The resultant heat of such laser-tissue interactions should be controllable in order to avoid damage of nearby normal structures (8).

In this study, we observed that when the output power, interval or duration was increased, not only did the recorded temperatures increase, but also the thermal distribution on the brain surface and volume of coagulation necrosis increased. Although there was not a linear correlation between applied joules of laser and macroscopic diameter of the induced lesion as other investigators had reported (3,9), the increase in denaturated volume were more consistent with increase in joule. Another striking finding was that the diameters of coagulation necrosis were much smaller than the corresponding size of thermographic heat distributions at the brain surface. Although the diameters of necrosis ranged between 1.5 and 8 mm macroscopically, the diameters of the thermograms (corresponding to 35.1°C) were between 15 and 30 mm. Also the temperatures recorded one cm away from the tip of the laser probe increased up to 35.8°C. Increases in brain temperatures of this magnitude in real patients may lead to neuronal damage or dysfunction in nearby normal tissues, although this type of damage has not yet been reported in the literature. So in planning denaturation of any lesion in the brain, there should be some safety distance to adjacent important neural and vascular structures in order not to damage them. For this purpose, although our laser probe was not appropriate for ITT, we believe that our results concerning physical changes, may be used as a guide.

If a lesion in the brain is to be denaturated in a single stage operation, in which the probe is placed in the center of it without changing its position, a large area of adjacent normal neural tissue will be heated. However, if the volume of the lesion is divided into smaller volumes, it may be denaturated portion by portion by moving the stereotactically-placed probe and varying the irradiating conditions. In this manner, heat distribution to surrounding tissues may be minimized, and potential complications avoided.

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