Stereotactically Guided Laser Therapy of Occult Breast Tumors

Work-in-Progress Report

Kambiz Dowlatshahi, MD; Ming Fan, MD; Victor E. Gould, MD; Kenneth J. Bloom, MD; Amjad Ali, MBBS

Hypothesis: Mammographically detected breast tumors can be completely ablated with laser energy.

Design: Nonrandomized control trial.

Setting: A university hospital ambulatory care center.

Patients: Thirty-six patients with mammographically detected well-defined breast tumors were selected.

Interventions: The diagnosis of malignant neoplasms and determination of prognostic factors were established by image-guided needle-core biopsy. Patients were treated on a stereotactic table, using a 16- to 18-gauge laser probe, with an optic fiber transmitting a predetermined amount of laser energy. A multisensor thermal probe was inserted into the breast adjacent to the laser probe to monitor treatment. In the last 10 patients, the tumor blood flow was evaluated before and after laser therapy with contrast-enhanced color Doppler ultrasound. One to 8 weeks after laser therapy, the tumors were surgically removed and serially sectioned.

Main Outcome Measure: Complete necrosis in 66% of tumors.

Results: Total tumor ablation with negative margins was observed whenever 2500 J/mL of tumor was given or the thermal sensors recorded 60°C. Microscopic examination at 1 week showed disintegration of malignant cells, with peripheral acute inflammatory response and at 4 to 8 weeks extensive fibrosis. Contrast-enhanced color Doppler ultrasound revealed loss of tumor circulation after therapy, and positron emission tomography scan correlated well with histologic findings. There were no systemic adverse effects. Two patients sustained 3 × 4-mm skin burns around the laser needle.

Conclusion: A stereotactically guided minimally invasive technique may be effective for the treatment of mammographically detected breast cancer.

Arch Surg. 2000;135:1345-1352

The widespread practice of screening mammography and the increasing awareness of women as to its benefits has resulted in a growing number of tumors smaller than 1 cm being detected. Diagnosis of these non-palpable breast tumors is made by stereotactic or ultrasound-guided core biopsy, a less invasive procedure than wire localization and excisional biopsy. Currently, the favored local treatment of such tumors is by lumpectomy plus either axillary node dissection or sentinel node biopsy followed by chemotherapy and/or radiation therapy. Less invasive image-guided techniques employing vacuum-assisted large needles or automated cannulae are potential alternatives. In situ ablation of tumors in solid organs, such as the liver and prostate, with laser energy, cryotechnology, or radiofrequency has been reported. The goals of this investigation were to evaluate a minimally invasive method of ablating mammographically detected breast tumors, determine its effectiveness and safety, and develop techniques of monitoring the ablating effect during and after the treatment. This article is a work-in-progress report on the evolving phases of this new procedure describing its technical and clinical feasibility; it is not our intention to compare it with lumpectomy or other excisional operations for treatment of early breast tumors. 

RESULTS

Demographic details of 36 patients with invasive (n = 34) and in situ (n = 2) breast tumors initially treated with interstitial laser therapy and subsequently excised for pathologic evaluation are shown in Table 1. Patients' age ranged from 42 to
PATIENTS, MATERIALS, AND METHODS

Thirty-six women of diverse socioeconomic and racial backgrounds with mammographically detected breast tumors were selected for this study. The selection criteria were as follows: invasive or in situ tumors up to 2 cm in the greatest diameter as measured on mammograms or by ultrasound, nonpalpable or minimally palpable tumors, with the nearest border 1 cm away from the skin or the chest wall, and the lesion boundaries circumscribed and visualized on 2 mammographic views for determination of tumor dimensions by imaging techniques (Figure 1).

Patients were invited to undergo initial treatment of their breast tumors with interstitial laser therapy before lumpectomy, axillary node dissection, and, more recently, sentinel node biopsy. The protocol was approved by the Rush Institutional Review Board and every patient gave a written permission after the nature of the study was fully explained to her.

The laser source was a semiconductor 805-nm diode laser (Diomed-25; Diomed, Cambridge, England). The laser fiber was a 400- to 600-µm–diameter quartz fiber with a spherical tip (SURGIMED, Woodland, Tex). The probe carrying the laser fiber was a prototype 16- to 18-gauge, 18-cm–long, stainless steel trocar with a stylet. A thermal sensor made of copper and Constanan (Republic Technology Inc, Charlottesville, Va) was soldered to the external surface of the laser probe to record the temperature of the heated tumor at the point of laser light emission. A y-shaped connector (Qosina, Edgewood, NY) was used to fix the position of the laser fiber, so that its tip protruded 2 mm beyond the tip of the trocar during treatment. A fluid pump (Trex Medical, Danbury, Conn) was attached to the second arm of the y-shaped connector to infuse normal saline at the rate of 0.5 to 2.0 mL per minute into the tumor. This would prevent the central temperature from exceeding 100°C and carbonization of the fiber tip, thus allowing more efficient light energy transmission to the tumor periphery.

The peripheral temperatures of the tumor during laser therapy were continuously recorded by a single 20-gauge multisensor thermal probe. This prototype probe had 5 sensors attached to its surface at 5-mm intervals and, when inserted into the breast parallel to and 1 cm away from the laser probe, it would display the tissue temperature from 1.0 to 1.4 cm in front and behind the laser fiber tip (Figure 2). At a later phase of our experience (from patient 18 onward) both laser and thermal probes were replaced with sturdier 16-gauge needles to eliminate deviation and to maintain correct spatial relations of the probes during insertion into the breast.

The central and peripheral temperatures were graphically displayed on a monitor and software was developed to interface the laser power input and fluid infusion with thermal sensors so that the central temperature was maintained between 80°C and 100°C, while the peripheral temperature rose to 60°C.

COLOR DOPPLER ULTRASOUND

From 1996 (patient 10 onward), contrast-enhanced color Doppler ultrasound was employed to evaluate the tumor blood flow before and after laser therapy. We used 7.5-MHz linear array transducer ultrasound (ATL, Bothel, Wash). Subsequent to a series of animal experiments, the echogenic contrast solution Albunex (Mallinkrodt, St Louis, Mo), 0.2 mg/kg of body weight, was given intravenously, but the desired effect was too transient (2-5 seconds) for maximal recommended dose of the contrast agent. Since 1997 (patient 20), we have used the ultrasound imaging agent Optison (Mallinkrodt) in a bolus of 0.5 mL intravenously. This has resulted in capturing superior images lasting 50 to 70 seconds. It has therefore been possible to record tumor blood flow before laser therapy and again before lumpectomy 1 to 8 weeks after treatment.

Figure 1. Craniocaudal (A) and mediolateral (B) mammographic views of an occult breast carcinoma.
POISON THERAPY

Preoperatively, patients were visited by an anesthesiologist. An intravenous line was set up for administration of light sedation. Vital signs were monitored during therapy. The patient then lay prone on the stereotactic table with the tumor-bearing breast protruding through the aperture. The treatment approach to the tumor was determined based on the following parameters: clear visualization of the lesion cranio-caudally, latero-medially, or from any other suitable angle; avoidance of intervening vessels; and the shortest route from skin to the target.

Based on the scout view, the position of the breast was adjusted so that the lesion was centered in the operating window of the stereotactic table. Stereograms were taken to determine the coordinates of the tumor. An additional 2 to 3 core biopsy specimens were taken from the tumor for determination of prognostic factors if these were not done previously. At this point the greatest diameter of the tumor and 0.5-cm cuff of breast tissue around it were again measured on the stereograms to calculate the volume (V) of the therapeutic sphere, according to the formula: $V = \frac{4}{3} \pi r^3$, where $r$ represents the radius of the tumor plus 0.5 cm of surrounding breast parenchyma. Based on our previous experimental observation, 1400 J of laser energy was needed for complete necrosis of 1 mL of tumor tissue.15,16 For example, a typical 1-cm tumor, with a 0.5-cm cuff of tissue measuring 4.2 mL, required 6000 J of laser energy.

At a later phase of our experience (patient 31), we marked the boundaries of the tumor, at the 3-, 6-, 9-, and 12-o’clock positions, with metal markers (Cook Corp, Bloomington, Ind) introduced through a needle. These markers would help us to identify the tumor boundaries during treatment when infusion of fluids and anesthetic agent might partially obscure the tumor. They would also serve as reference points for future sampling of the tumor margins.

The skin at the site of the laser and thermal probes entry was infiltrated with 1% lidocaine, and field anesthesia around the axis of the laser probe was achieved with 0.5% bupivacaine. Through 2 skin nicks, the laser and thermal probes were inserted into the breast. The lines were connected to the laser source, fluid pump, and the thermal monitor. Stereograms were taken to ensure that the laser probe tip was in the center of the tumor and that the thermal probe was parallel to the laser probe, with its tip 1 cm in front of the latter (Figure 3). Patient and attendants wore protective laser goggles. The treatment was then begun by first infusing 1 mL of normal saline before switching on the laser at 5 W; it was then raised to a 10-W power setting (for faster treatment) to deliver the predetermined amount of energy to the tumor. The central and peripheral temperatures were displayed continuously on a monitor. Patients were given additional local or intravenous analgesia if they experienced pain. The average duration of treatment was 20 minutes, and the end point was reached when all thermal sensors recorded $60^\circ$C; postlaser therapy stereoradiographs were then taken. The probes were removed and the breast was decompressed. Patients’ vital signs were monitored for 1 hour and then they were discharged home with oral analgesics and an ice pack on the breast.

Between 1 and 8 weeks later, patients were recalled and tumor blood flow was again reassessed with image-enhanced color Doppler ultrasound (10 patients) and PET scan (4 patients).

All patients underwent wire localization and lumpectomy followed by axillary node dissection, and, more recently, sentinel node biopsy. One patient underwent mastectomy. Postoperatively, all patients received appropriate doses of radiation therapy to the breast, and, whenever indicated, chemotherapy, as part of their adjuvant treatment.

80 (mean, 60) years. The tumor size as recorded by the greatest diameter on prebiopsy mammogram and ultrasound ranged from 5 to 20 mm (mean, 12 mm). Two patients, both with the diagnosis of ductal carcinoma in situ, presented with microcalcifications. The remaining 34 patients presented with suspicious masses. Image-guided needle-core biopsy confirmed the diagnosis of invasive ductal carcinoma in 29 patients, invasive lobular carcinoma in 5 patients, and ductal carcinoma in situ in 2 patients. The actual amount of laser energy given to cause ablation of the tumor ranged from 2500 to 10000 (mean, 5650) J. This was generally less than the planned amount of energy for an average tumor with 12-mm diameter plus a 10-mm safety zone around it. The radius of such a target is 11 mm, the calculated volume is 5.5 mL, and the amount of laser energy, based on experimental data of 1400 J/mL, is 7700 J. The overriding factor for giving less laser energy was the recording of $60^\circ$C by all peripheral thermal sensors. The size of the coagulated tissue, as measured by the diameter of the hyperemic zone on pathology sections

Figure 2. Sketch of a breast cancer with associated laser and thermal probes. The laser probe with an attached thermal sensor (Tc) recorded the central temperature. The multisensor (T1-T5) thermal probe recorded the temperature of concentric zones around the tumor.
of the resected tumor (Figure 4A), ranged from 10 to 27 (mean of 18) mm. Pathologic examination of the excised laser-treated tumors revealed complete necrosis of the tumor with negative margins in 24 patients and with residual tumors in 12 patients. Residual tumor is defined as a rim of a small island (1-3 mm) of viable malignant cells always on the periphery or outer boundaries of the main mass, having conventional microscopic appearance of ductal or lobular carcinoma. Table 2 summarizes the reasons for these failures. In the first 4 patients, who were treated during the learning phase of this new therapy, we proceeded with much caution, delivering suboptimal laser energy to the breast tumor—an average of 3800 J instead of 6000 J—as had been calculated. As we gained experience and confidence, we gave the tumors of the next 9 patients greater amounts of energy, resulting in complete necrosis with clear margins. The average amount of laser energy given to this subset of 9 patients was 6200 J, resulting in mean necrotic diameter of 17 mm and volume of 2.5 mL, suggesting that 2500 J/mL was required for complete tumor ablation.

The residual tumors in patients 14 and 32 were attributed to patients being oversedated, which led to excessive patient movement and laser-probe displacement. During the third year of our experience, substantial technical changes were made. Both the laser and the thermal probes were redesigned and larger needles (gauge 16 vs gauge 18) were employed to avoid bending of the probes during insertion. The infusion pump was changed and the system was semiautomated employing a computer. During this phase of our experience 3 patients (patients 19, 20, and 25) exhibited positive margins at lumpectomy. It was also during this period that 2 patients sustained full-thickness skin burns around the laser probe, which measured 3 to 4 mm. The next 2 failures were because of the operators’ inability to precisely visualize the tumors at the time of the probe insertion. The tumor boundaries of patients 26 and 28 were ill-defined and the laser probe tip was off-center, resulting in lopsided coagulation and a 1- to 3-mm crest of tumor escaping ablation. Finally, in 1 patient (patient 30), the tumor size was 2 cm, and a thin rim of cancerous tissue at the periphery of the tumor escaped coagulation. This patient’s case demonstrates the limitation of the therapy when only 1 pass is made.

**THERMOMETRY**

Continuous thermal monitoring of the laser-treated tumors were made in all patients. The central thermal sensor responded immediately on starting of the laser therapy, displaying 10°C to 30°C rise before the peripheral sensors recorded the heat effect, usually within 20 seconds. The sensors closest to the laser fiber (Figure 2) showed higher numbers than those 1.2 to 1.4 cm further away. The final figures at the completion of therapy were usu-
ally 80°C to 100°C for the central sensor and 60°C or higher for peripheral thermal sensors.

ULTRASOUND

Contrast-enhanced color Doppler sonography of uncompressed breasts showed the tumor blood flow within and around the tumor before laser therapy and none in the treated zone afterward (Figure 5). Histologic examination of the resected tumor revealed the thrombosed vessels within the coagulated zone, which corresponded to the sonographic “black hole.”

PATHOLOGIC FINDINGS

Macroscopic examination of the laser-treated tumors showed 2- to 5-mm central necrosis, with focal carbonization corresponding to the site of the laser fiber tip. This area was surrounded by concentric zones of coagulation necrosis and an outer inflammatory ring (Figure 4A). Microscopic examination at low power revealed an inner zone of “mummified” malignant cells, in which the lesion’s architecture and cellular “ghosts” could be recognized by hematoxylin-eosin staining (Figure 4B). Malignant cells exhibited severe signs of nuclear and cytoplasmic disruption; important molecular components were no longer detectable by immunohistochemistry.18 Depending on the interval between treatment and resection of the tumor, the outermost zone consisted of acute inflammatory cells and new capillaries (1 week after laser therapy) or granulation tissue and fibrosis (4-8 weeks after therapy). Extravasation of blood and vascular thrombosis were also evident throughout the coagulated zone.

PET SCAN

Four patients underwent PET scan to evaluate the monitoring utility of this technique before and 2 weeks after laser therapy. The isotope uptake was evident in all 4 patients before treatment. After laser therapy, the uptake was weakly positive in 3 patients and absent in 1. The pathologic examination of all 3 positive patients revealed residual tumor; none was seen in the fourth patient, in whom no activity was noted by PET scan. This is a very limited observation with a highly sophisticated and expensive imaging technique, but is nevertheless worthy of further study.

LOCAL AND SYSTEMIC EFFECTS

Retrograde flow of hot fluid along the tract of laser probe caused slight scalding and discomfort during therapy, necessitating the application of coolant fluid and an ice pack. Two patients sustained 3 × 4-mm skin burns around the entry point of the technically faulty redesigned laser probes, which were subsequently corrected. These were excised at the time of lumpectomy with no delayed effect. During the immediate postlaser therapy and the ensuing 48 hours, patients experienced minimal local pain, warmth, and sensation of heaviness in the breast. There was no incidence of bleeding or infection of the treated breast requiring intervention or administration of anti-

Table 2. Analysis of 12 Patients With Residual Tumor After Laser Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3, 4</td>
<td>Inadequate laser energy (learning phase)</td>
</tr>
<tr>
<td>14, 32</td>
<td>Oversedated patients, excessive movements</td>
</tr>
<tr>
<td>19, 20, 25</td>
<td>Technical failure: malfunctioning thermal probes</td>
</tr>
<tr>
<td>26, 28</td>
<td>Suboptimal target visualization because of excessive fluid infusion (patient 26), hematoma after needle biopsy (patient 28)</td>
</tr>
<tr>
<td>30</td>
<td>Large tumor (2 cm)</td>
</tr>
</tbody>
</table>
Detection of small breast tumors by screening mammography and the emergence of image-based percutaneous biopsy techniques have dramatically changed the diagnosis and treatment of breast cancer. The diagnostic tools, such as vacuum-assisted needles and automated cannulae with a cutting device, allow the physician to remove larger volumes of the suspicious tissue, and, not infrequently, the entire target. Thus, percutaneous diagnostic biopsy is moving into image-guided therapy. In situ ablation of small breast tumors by freezing or heat may also prove effective, as shown in other solid organs. Cryotherapy of liver metastases and prostate and breast cancer has been reported. Similarly, radiofrequency energy has been employed for destruction of malignant tumors in the liver, prostate, and breast. Application of laser energy for coagulation of breast tumors via an optic fiber is an appealing concept that was first described by Bown in 1983. Subsequently, several groups successfully demonstrated in situ ablation of hepatic and palpable breast tumors.

The introduction of stereotactic technology in the United States in 1986 enabled physicians to diagnose non-palpable breast tumors with a high degree of precision. The use of this technology for delivery of ablative laser energy to the target tumor within the breast was a logical extension of its application. Our group developed and tested the technique in the laboratory and found that chemically induced tumors could be totally coagulated with 1 pass of a laser probe into the center of a 2-cm rodent mammmary tumor. It was also noted that 1400 J of laser energy was adequate to coagulate 1 cm³ of the tumor, provided the temperature reached 60°C. The laser energy is chiefly converted into heat, which spreads centrifugally. Some energy also reaches the tumor cells by radiation.

With this information in hand, 62 liver metastases in 26 patients were treated. Tumors 2 cm or smaller were converted into scars, but those larger than 2 cm recurred after the initial regression. Systemic adverse effects consisted of transient pyrexia and minimal elevation of liver enzyme levels. Other investigators reported similar findings and noted that destruction of larger tumors could be achieved with insertion of multiple laser fibers. In 1994, Harries et al also reported on ultrasound- and computed tomography–guided interstitial laser therapy of breast tumors.

Our group previously reported on a series of 8 patients with mammographically detected breast cancer initially treated with stereotactically guided laser therapy and subsequently excised for pathologic evaluation. Over the past 4 years, several technical refinements have been made and implemented to achieve efficient delivery of the laser energy for complete ablation of the target tumor. The results of this investigation show that breast tumors smaller than 1.5 cm, either detected by mammography or quasipalpable, may be completely destroyed within the breast by percutaneously transmitted laser energy via an optic fiber placed inside a needle and stereotactically guided to the center of the tumor. The prognostic factors are determined on needle core samples obtained before laser therapy. The procedure may be performed under local anesthesia in an outpatient setting. This technique can be applied for treatment of a subset of invasive and in situ ductal carcinoma of the breast with fairly well-demarcated boundaries, as shown in Figure 1. However, tumors with undefined borders, invasive lobular carcinoma, and scattered microcalcifications (representing extensive ductal carcinoma in situ) are unsuitable, and tumors close to the surface (<1 cm) or the chest wall may result in skin necrosis or intractable skeletal pain.

**TARGETING**

Good visualization of the tumor and placement of the fiber tip in its center are essential for total tumor “kill.”
To achieve this goal, metallic markers are inserted around the tumor before infusion of anesthesia. This would ensure target identity at the time of fiber placement and future evaluation of the treated tumor. Placement of the laser fiber tip in the tumor center is also essential, because that will provide symmetrical heat distribution. A coagulative sphere with a 2.0- to 3.0-cm diameter would encompass a 1.0- to 1.5-cm tumor and a 0.5-cm ring of tissue around it.

**MONITORING**

Real-time visual evaluation of the tumor during laser therapy is ideal. However, the acute changes are not detected by stereotactic digital images. Sonography of the tumor during treatment shows microbubble formation and increased echogenecity on the Gray scale but does not accurately delineate the extent of tumor destruction. Magnetic resonance imaging with special breast coils provides good images of breast tumors. The thermal changes, appearing as a nonenhancing zone, are optimally seen 1 to 4 days after treatment. Our limited experience with PET scan shows good prediction for tumor ablation, but it is suspected that an interval of several weeks is needed before the tumor isotope uptake can be differentiated from hyperemia induced by laser burn. Our preliminary observation with contrast-enhanced color Doppler sonography reveals loss of blood flow to the tumor after laser therapy leading to necrosis (Figure 5). The size of the devascularized area corresponds to the coagulated lesion seen on histologic sections (Figure 4). Clearly, this is a simple and practical test for evaluation of the laser-treated tumor and may be applied in conjunction with thermometry. Continuous recording and display of tumor temperature centrally and peripherally have guided us as to the adequacy of laser therapy. The treatment end point is reached when either all peripheral temperatures exceed 60°C or the predetermined amount of energy is given. The data from this series indicate that 2500 J/mL of target lesion resulted in total coagulation with negative margins. Contrast-enhanced color Doppler ultrasound will then delineate the loss of blood flow to the tumor and a 0.5-cm cuff of surrounding breast tissue.

**CONCLUSIONS**

Interstitial laser therapy is a novel method of in situ ablation of a well-defined subset of mammographically detected breast tumors. To our knowledge, this is the first report of an extended series of patients treated in this manner. With widespread availability of stereotactic technology and surgeons trained in the art of image-guided breast biopsy, it is expected that image-based surgery for small malignant and benign breast tumors will provide the patient with a less painful and aesthetically more pleasing therapeutic modality. We plan to invite surgeons specializing in breast cancer to participate in this clinical trial to expand the experience as outlined in this article before moving on to the next phase of prospective trial comparing this technique with lumpectomy or other minimally invasive techniques.

Supported by grants from Brian Piccolo/Chicago Bears Research Foundations, Chicago, Ill, and Mary Kay Ash Charitable Foundation, Dallas, Tex, and technical and financial support from the Lorad Corporation and Trex Medical Corporation, Danbury, Conn (Dr Dowlatshahi).

We thank Eulonda Lacy for her assistance in preparing this article.

**REFERENCES**


ARCHIVES OF INTERNAL MEDICINE

Epidemiology of Restless Legs Symptoms in Adults

Barbara Phillips, MD, MSPH, FCCP; Terry Young, PhD; Laurel Finn, MS; Karen Asher, BA; Wayne A. Hening, MD, PhD; Cheryl Purvis, PhD

Background: Restless legs syndrome (RLS) is a disorder characterized by sleep-disrupting unpleasant leg sensations, often accompanied by daytime behavioral problems. Treatment for this condition is available, but it is suspected that most instances of RLS remain undiagnosed. The goal of this investigation was to assess the prevalence and health status correlates of restless legs symptoms (hereinafter referred to as restless legs) in the general population.

Methods: A question reflecting the clinical features of RLS was added to the 1996 Kentucky Behavioral Risk Factor Surveillance Survey. Data on the frequency of experiencing restless legs, self-rated general and mental health status, demographics, and behavioral risk factors were collected by telephone interview from 1803 men and women, 18 years and older.

Results: Experiencing restless legs 5 or more nights per month was reported by 3% of participants aged 18 to 29 years, 10% of those aged 30 to 79 years, and 19% of those 80 years and older. The age-adjusted prevalence for Kentucky adults is 10.0%; prevalence did not vary significantly by sex. The adjusted odds ratios (95% confidence intervals) for restless legs and diminished general health and poor mental health status were 2.4 (1.4-4.0) and 3.1 (2.0-4.6), respectively. Restless legs were significantly associated with increased age and body mass index, lower income, smoking, lack of exercise, low alcohol consumption, and diabetes.

Conclusions: The prevalence of restless legs in the general adult population is high. Restless legs may be associated with decreased well-being, emphasizing the need for further research and greater medical recognition of this condition. (2000; 160:2137-2141)

Reprints not available from the authors.