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Focus On

Shift in the surgical treatment of non-palpable breast cancer: tactile to visual

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Abstract Increasing number of small, early-staged breast cancers are detected by screening mammography. Diagnosis and determination of the prognostic factors may be made by either ultrasound (US) or stereotactically guided needle biopsy. Approximately 2000 stereotactic tables are installed at various medical centers throughout the United States and a significant number in other countries where breast cancer is common. Many surgeons and interventional radiologists are trained in the use of this technology for diagnostic purposes. Employing the same technology, these physicians may be trained to treat selected breast cancers with laser energy percutaneously. Experimental and clinical reports to-date indicate the technique to be safe. High-resolution imaging modalities including grayscale and color Doppler US, magnetic resonance imaging, mammography and needle biopsy, when necessary, will confirm the tumor kill. Newer imaging modalities such as magnetic resonance spectroscopy may also provide additional confirmation for total tumor ablation.

Keywords: Carcinoma of the breast; Interstitial laser therapy; Lumpectomy; Magnetic resonance spectroscopy; Mammography; Ultrasound

Introduction

The modern practice of medicine has increasingly become image-dependent. This is due to the advances in imaging technology: X-ray, ultrasound (US), magnetic resonance imaging (MRI), enabling the physician to find the disease, especially cancer, at an earlier stage of development and to initiate its eradication before spread. Screening mammography detects breast cancer at a non-palpable stage and diagnosis is made by image-guided needle biopsy. Less invasive and more image-dependent treatment techniques are the logical sequence of this trend. This shift has happened in other disciplines: angioplasty in lieu of open heart surgery, laparoscopic and arthroscopic procedures, and laser operations of the eye to correct the lens and to re-attach the retina.

In 1985, stereotactic needle biopsy technology was introduced into the USA for diagnosis of mammographically detected breast cancers and since then it has largely replaced open biopsy [1,2]. The logical extension of this technique is its therapeutic application. Thus the tumor can be ablated in-situ with a stereotactically guided needle, carrying a laser fiber directing the ablative energy to its center. The coagulated tumor is converted into a scar or a cyst by the body's immune system. The procedure is performed under local anesthesia in an outpatient/office setting at a lower cost. It is less painful and cosmetically superior to conventional surgery. The stereotactic device is available in most medical centers in US and Europe and requires short additional training of breast surgeons and interventional radiologists for its therapeutic application.

The goal of this communication is to present evidence that advanced breast imaging techniques are available for the physician to visually evaluate the extent of laser ablated tumor without its surgical

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removal. The technology also provides the means of monitoring for recurrence of the tumor and appropriate intervention.

Rationale

Heat kills cells

Boiling water scalds the skin, burns the tongue and destroys bacteria. The mechanism of destruction is due to cell membrane disruption, disintegration of the intracellular organelles and the cell nucleus. The principle of interstitial laser therapy (ILT) is based upon the conversion of light energy into heat which makes the water boil within the targeted tumor. Laboratory [3,4] and clinical [5,6] experience have shown that by precisely placing a thin optical fiber in the center of a small breast cancer and transmitting laser light at infrared range, small cancers are totally destroyed. The generated heat spreads centrifugally; creating a spherically-shaped mass of necrotic tissue measuring 2.0–3.0 cm in diameter (Figs. 1 and 2). Both normal and tumor cells within this zone are destroyed. This novel method of breast cancer treatment is applicable to mammographically detected clearly visualized tumors measuring up to 1.5 cm. The rest of the patient's breast cancer treatment that is lymph node sampling, radiation and chemo-hormonal therapy remain unchanged although some of them for example, radiation therapy is also undergoing change.

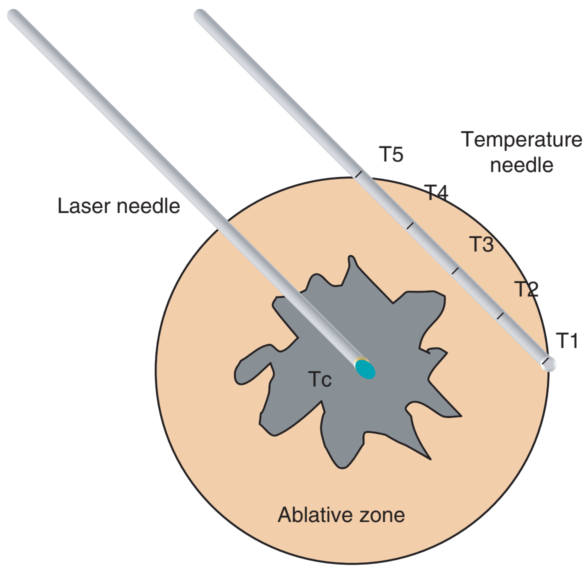

Figure 1.
Sketch of a malignant tumor with the tip of the laser probe in its center and the multi-sensor thermal probe 1 cm away and parallel with the laser probe. The laser heat causes a 2.5 cm necrotic zone when all thermal sensors record 60°C.

Background

With widespread practice of screening mammography in the USA, it is estimated that over 50% of breast cancers are detected smaller than 1 cm in diameter (Fig. 3). The majority of these cancers are seen as masses, clusters of microcalcifications or tissue densities. The diagnosis of malignancy is made by image-guided needle biopsy and increasingly the prognostic factors are also determined from the needle samples. The current surgical treatment for such cancers is

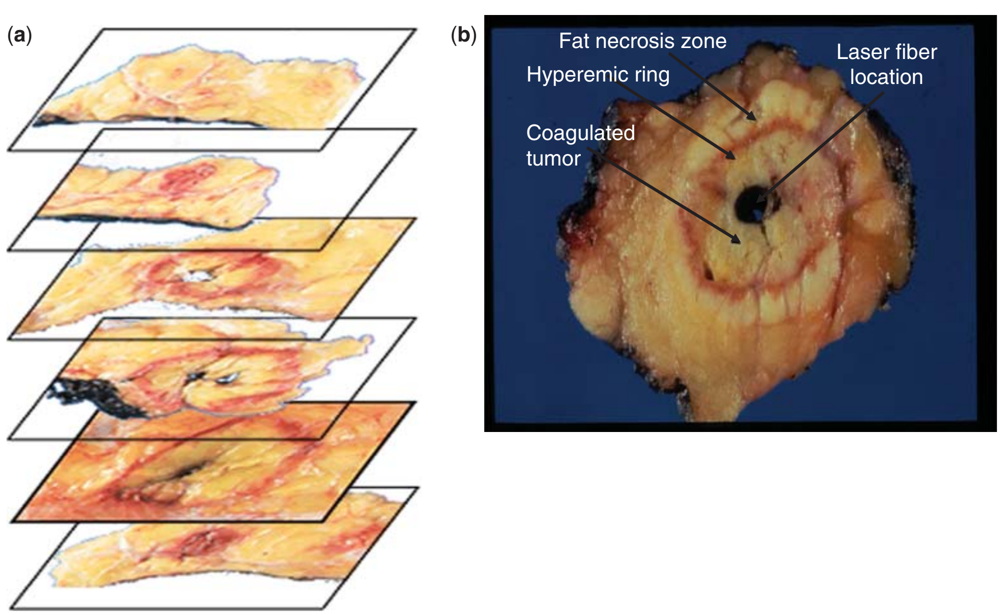

Figure 2.
*(**a**) Serial sections of a laser treated breast cancer, (**b**) Close-up view of a section showing from outside: fat necrosis, hyperemic ring, the coagulated tumor and the location of the laser probe.*

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wire-localization and lumpectomy. Either sentinel or axillary lymph nodes biopsy is employed to determine the extent of the regional spread (staging). The surgical removal of these small breast cancers, although adequate, remains the same as for larger tumors detected by the woman herself. A less invasive method of treatment for such tumors is more appropriate. This is especially true with 'baby boomers', which in their fifties, currently form a population bulge at the highest risk for breast cancer. These women are educated, very health conscious, have access to the Internet and seek the most advanced and least invasive means of diagnosis and treatment for breast cancer. In-situ ablation with laser serves this goal. There are close to 2000 stereotactic tables installed at various medical centers in the USA for diagnosis and many surgeons and radiologists are trained in the use of this technology. Application of this readily available technology and the corps of trained physicians for treatment of the mammographically detected breast cancers appear to be the logical sequence of this development.

Clinical experience

Since 1988 the author has been engaged with the development of interstitial laser therapy for treatment of a selected subset of breast cancer patients. Having developed the basic technique and gained experience in treating patients with liver cancer, the author began treating women with breast cancer under an institutional review board (IRB) approved protocol. Between 1994 and 2000, 54 patients from Rush University and Cook County Hospital breast screening clinics in Chicago volunteered to undergo laser therapy prior to definitive surgical treatment of their mammographically detected cancers. The treatment was delivered on a standard LoRad stereotactic table. The laser source was a semi-conductor diode laser at 805 nm wave length incorporated in a prototype device. The details of this experience were periodically published [5–8] as well as presented at scientific forums.

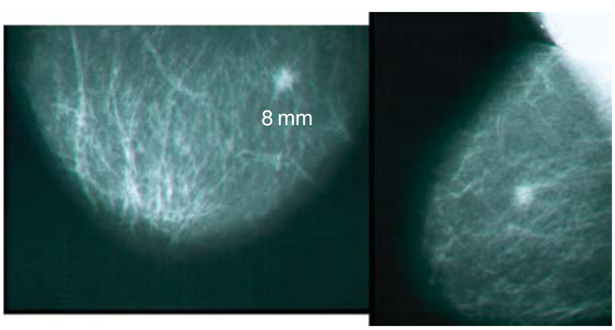

Figure 3.
Case No.1: Mammographically detected breast cancer.

Having gained technical proficiency and established the parameters for adequate therapy, under a new IRB protocol, seven patients with mammographically detected, needle core biopsy proven, invasive carcinoma were treated with ILT. The prognostic factors were determined on the core samples and the tumor blood flow was evaluated by color Doppler US pre- and post-laser therapy (Fig. 4). Pre-determined amount of laser energy was given under local anesthesia on a stereotatic table via a needle inserted into the center of the tumor until the peripheral temperature, measured by a multi-sensor thermal needle inserted 1 cm adjacent to the laser needle, reached 60°C (Fig. 5). After 1–2 h of observation patients were discharged home with ice-pack on the treated breast and oral analgesics. Patients were examined at 1, 3 and 6 monthly intervals with US and mammography. Needle biopsies were taken from five marked locations of the tumor at 1 month (Fig. 6). The follow-up ranged from 24 to 63 months. Full account of these cases will be published at a later date. However, to illustrate the role of modern breast imaging, a brief description of three cases is given below.

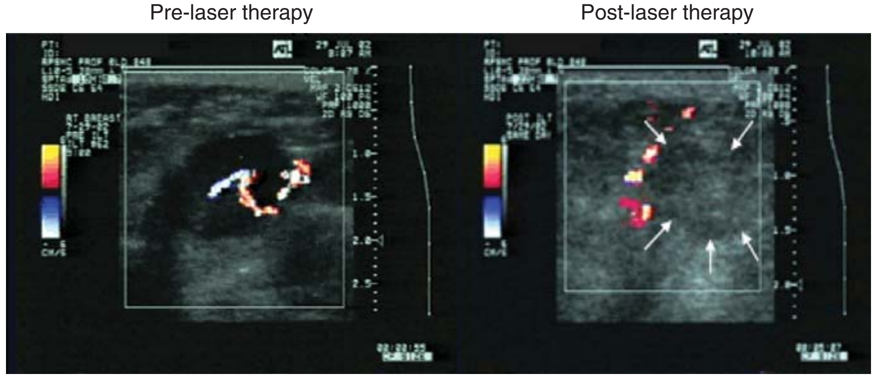

Figure 4.
Color Doppler images of a laser treated tumor demonstrating the loss of blood circulation within the tumor leading to its necrosis.

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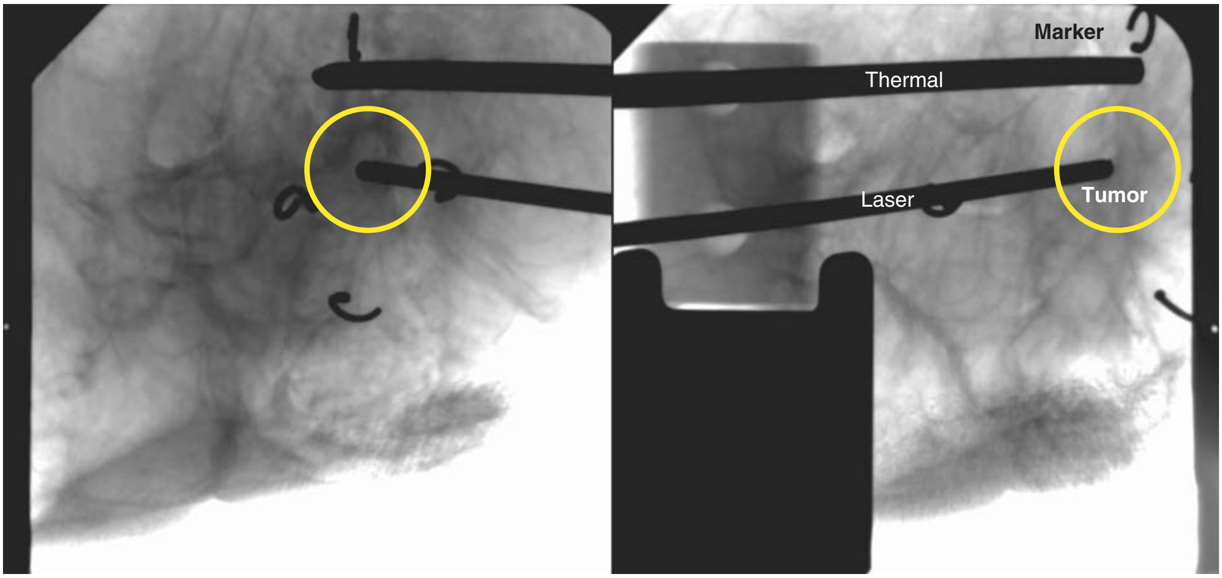

Figure 5.
Stereotactic image of the two probes in breast with four metal markers inserted around the tumor for follow-up reference.

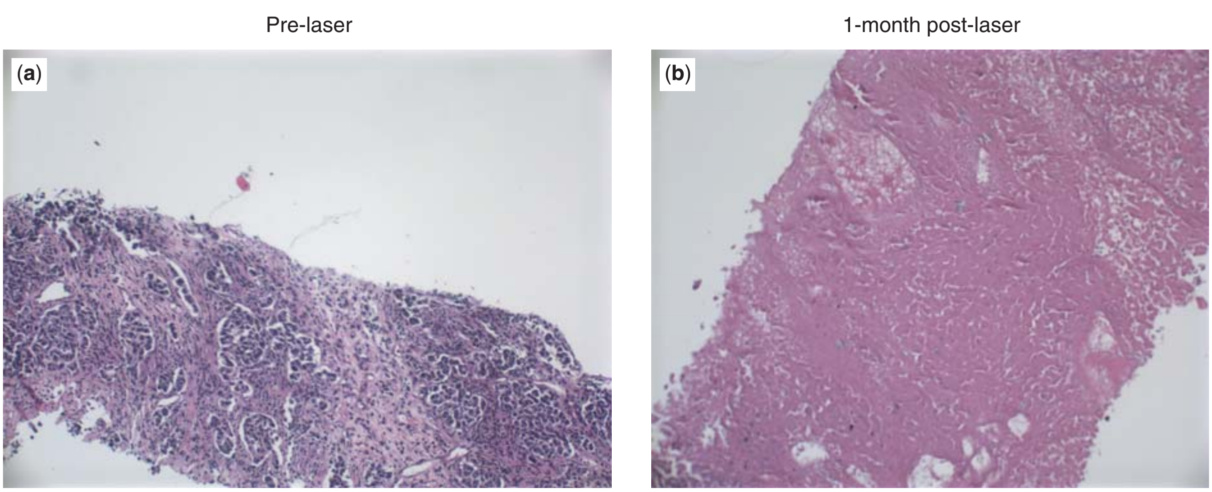

Figure 6.
*Needle core biopsy histology of invasive ductal carcinoma: (**a**) Pre- and (**b**) Post-laser therapy.*

Case 1

In February 2000, the annual mammography of a 70-year-old woman, in excellent health, was reported to show a new ill-defined 7 mm nodule in the left breast (Fig. 7**a**). Five years prior to this date, the patient's left breast carcinoma had been treated with lumpectomy, axillary node dissection, and radiation therapy. On this visit the suspicious lesion appeared to be in the same quadrant as the previous cancer. Stereotactic needle core biopsy of the nodule confirmed the diagnosis of low-grade invasive carcinoma with positive hormone receptors. Metastatic investigation was negative. The patient did not wish to undergo partial or total mastectomy and chose to have IRB approved laser treatment of the tumor without excision. She was treated on a stereotactic table with laser. During the first week, patient experienced minimal discomfort in the breast and slight swelling of the treated area. At 1 month she was free of any symptoms and mammogram at 6 months revealed that the tumor had shrunken (Fig. 7**b**). Stereotactically guided needle core biopsies taken from the center and four points around the treated tumor showed chronic inflammation and fat necrosis. The patient was placed on Tamoxifen tablets, 20 mg daily and was followed at 3, 6 months and semi-annually thereafter. Over the ensuing 18 months a painless cyst developed at the treatment site (Fig. 7**c**), which was percutaneously

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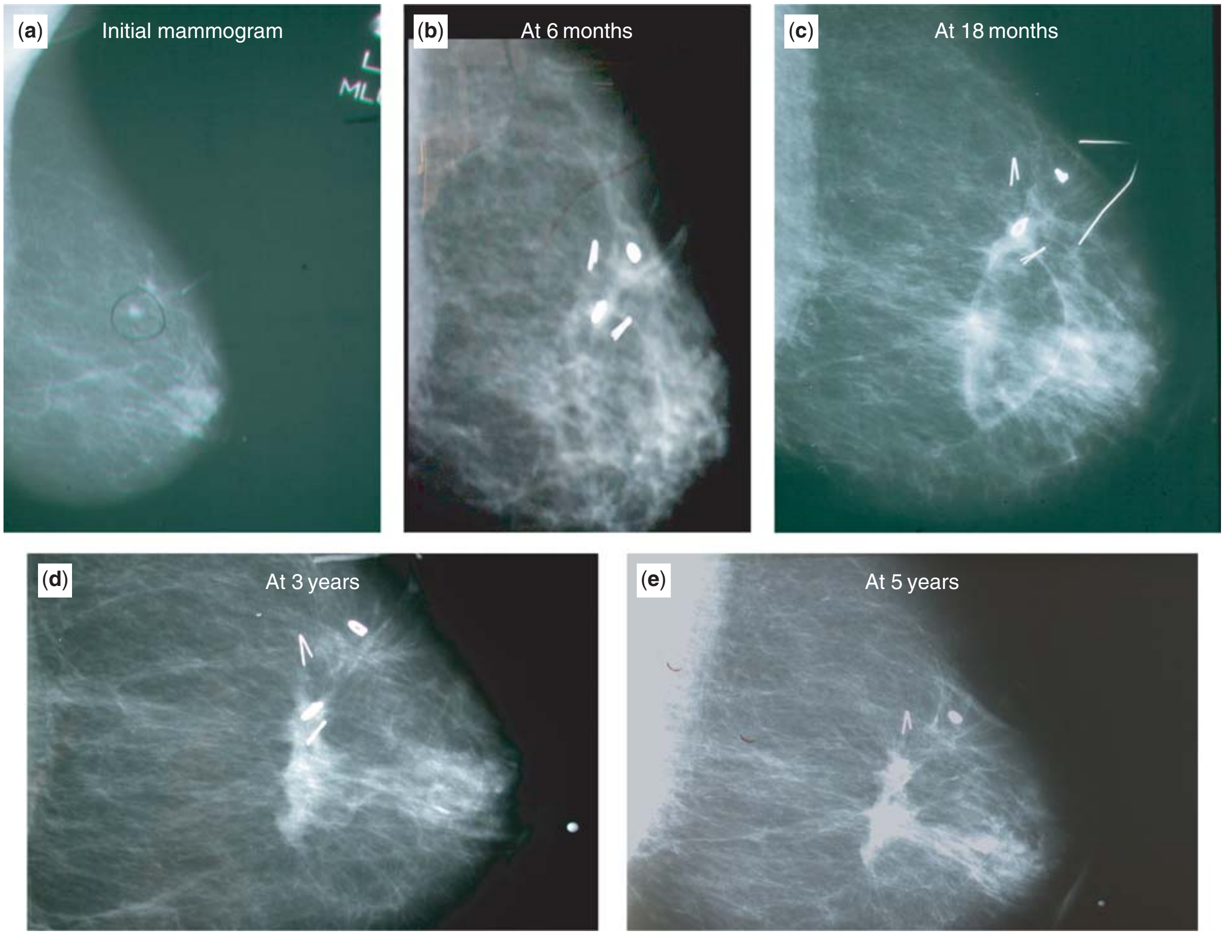

Figure 7.
*Serial mammograms of case No. 1 (**a**) the initial presentation (**b**) necrosis at 6 months, (**c**) cyst formation, (**d** and **e**) stability with no evidence of recurrence at 3 and 5 years post-laser therapy.*

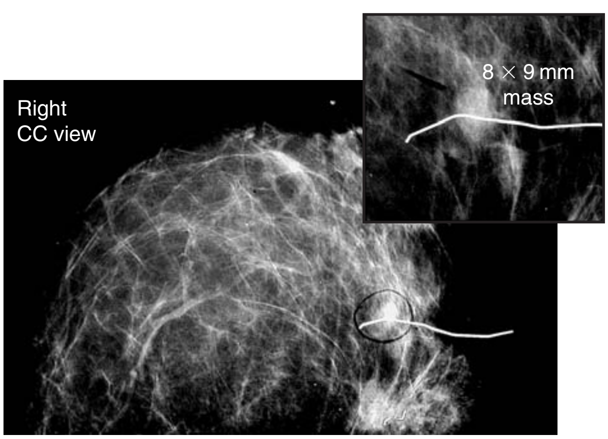

Figure 8.
Case No. 2: Annual mammogram showing a new suspicious nodule in the right breast.

aspirated. Cytology of the fluid showed no malignancy. Stereotactically guided needle biopsy of a questionable nodule in the wall of this cyst was also shown to be scar tissue. She continued to do well and has no evidence of local or systemic recurrence of breast cancer at 63 months (Fig. 7(**d**) and (**e**)), [8].

Case 2

A 61-year-old woman whose right breast carcinoma had been treated with partial mastectomy and irradiation 9 years earlier, was noted to have a new suspicious mass in the upper outer quadrant of the same breast, close to the site of the primary, on annual mammography (Fig. 8). Stereotactic needle core biopsy revealed invasive ductal carcinoma, grade I with positive hormone receptors and negative Her2neu. Metastatic work up was negative. Patient did not wish to undergo mastectomy and requested laser therapy. This was successfully performed in March 2002 on a stereotactic table under local anesthesia. No complication was encountered. Patient was placed on close surveillance at 1, 3, 6, 12 month and then semi-annually with imaging examination using US, mammography and in one occasion with an image-guided needle biopsy. Of particular interest was the formation and the maturation of a fibrous

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ring separating the ablated tissue from the normal parenchyma. This could be better visualized by US at 1 month (Fig. 9) and by both modalities from 3 months onwards. These images (Figs. 9–12) clearly show how a laser ablated tumor may be put under surveillance. Breast US at 36-month post-ILT revealed a suspicious 8 mm mass which on needle biopsy was shown to be invasive carcinoma. On reviewing the color Doppler images of the breast taken at 30-month post-treatment, it was noted that a cluster of new capillaries had developed prior to the appearance of the cancer (Fig. 13). This lesion was wire-localized and excised together with the adjacent laser treated necrotic tissue. Pathology showed the tumor size and its US image to match perfectly (Fig. 14). Again the metastatic work up was negative and the patient decided against mastectomy. She was placed under close imaging surveillance and

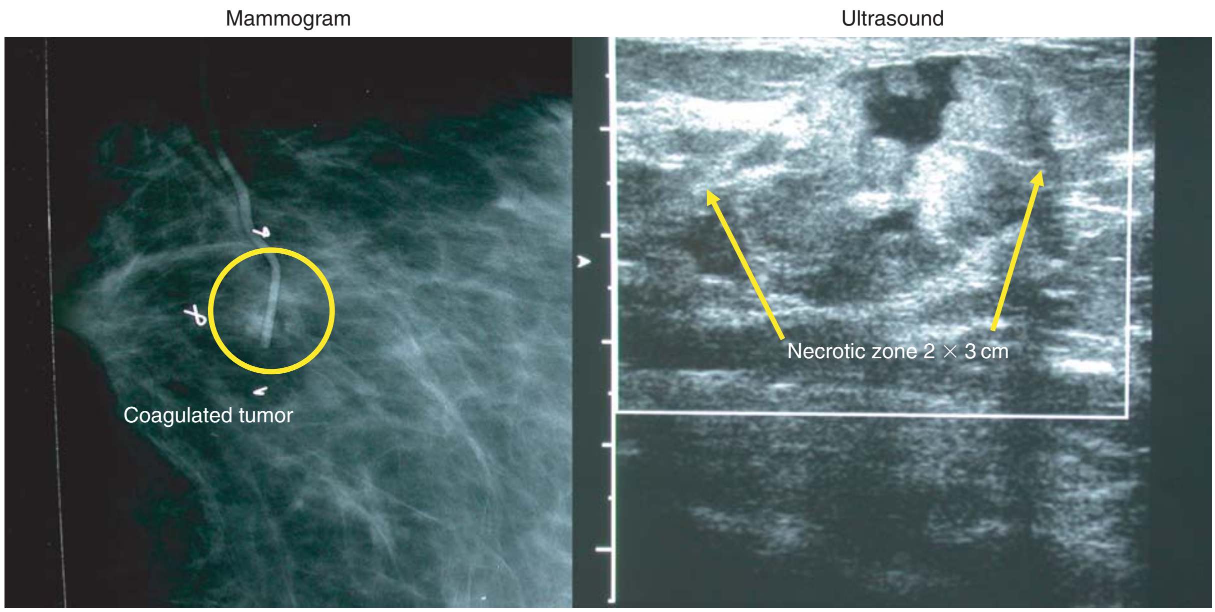

Figure 9.
At 1 month, the coagulated tumor is poorly visualized by mammogram, but is well demarcated by US.

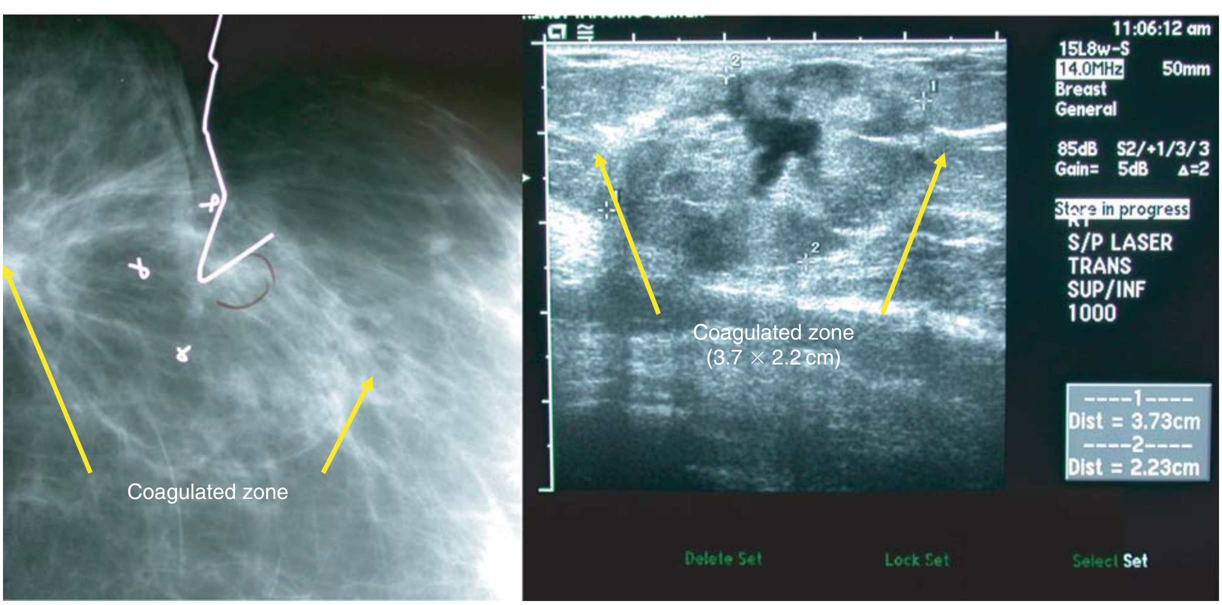

Figure 10.
At 3 months, the oval-shaped coagulated tissue can be seen both by mammography and US. Note partially liquefied center on US image.

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was advised to take Arimidex tablets 1 mg daily as the hormone receptors of the recurrent tumor were strongly positive.

Case 3

A 41-year-old woman whose right breast carcinoma had been treated with lumpectomy and irradiation in April 2000, was noted to have developed a suspicious mass in the contra-lateral breast on annual mammogram of August 2003 (Fig. 15). At this time patient wished to have laser treatment of the left breast cancer despite its large size of 22 mm with the proviso that surgical excision will be performed if residual carcinoma was noted on follow-up images. Indeed MRI of the left breast 4 weeks after laser therapy revealed a suspicious focus of malignancy (Fig. 16), confirmed by image-guided needle core biopsy (Fig. 17). Patient underwent partial mastectomy and the resected specimen was serially sectioned at 3 mm intervals. A focus of viable carcinoma immediately adjacent to the necrotic border of the laser treated tumor was found measuring 9 mm matching the MRI image (Fig. 18). Patient was treated with adjuvant chemo-radiation therapy according to the current protocols. She is well and without evidence of recurrence two years later.

Comments

The goals of this communication are two fold. First, it is intended to draw the attention of oncologists

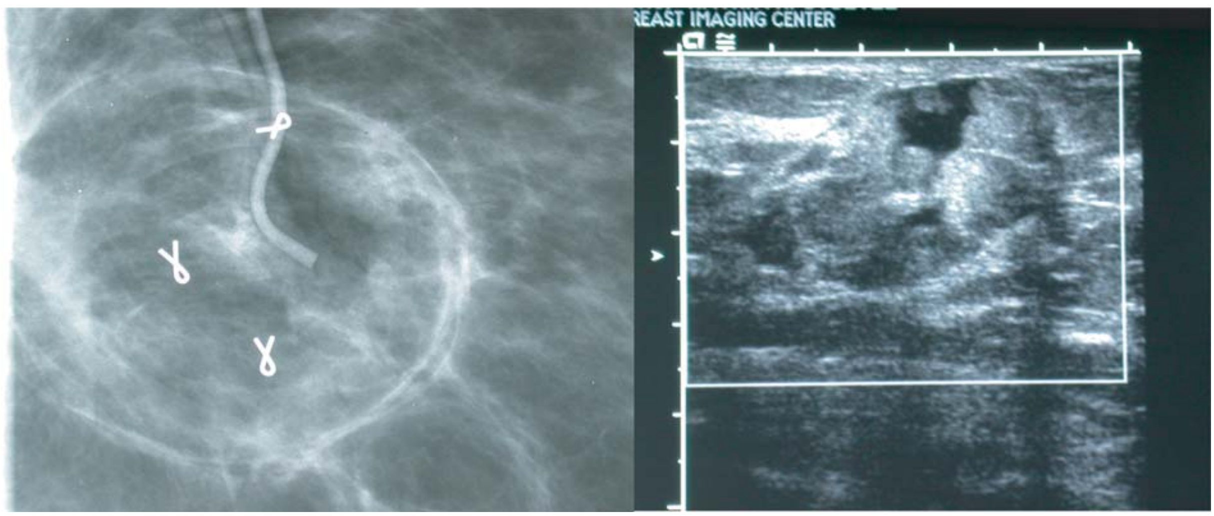

Figure 11.
At 12 months, the fibrous ring around the necrotic zone is mature and well visualized by mammography.

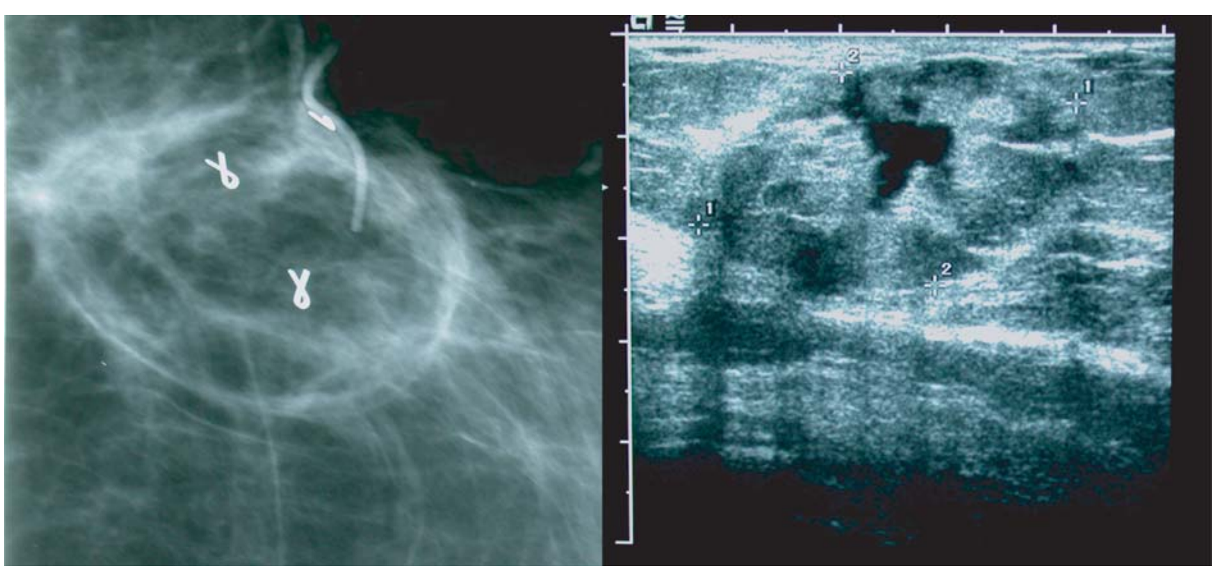

Figure 12.
At 24-month post-treatment, there is no evidence of recurrence.

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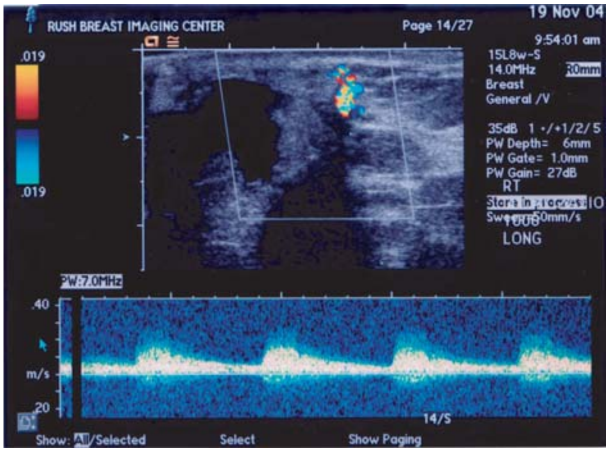

Figure 13.
At 30 months an irregular hypoechoic suspicious mass with neo-vasculature appeared immediately adjacent to the necrotic zone. Needle biopsy confirmed recurrent ductal carcinoma.

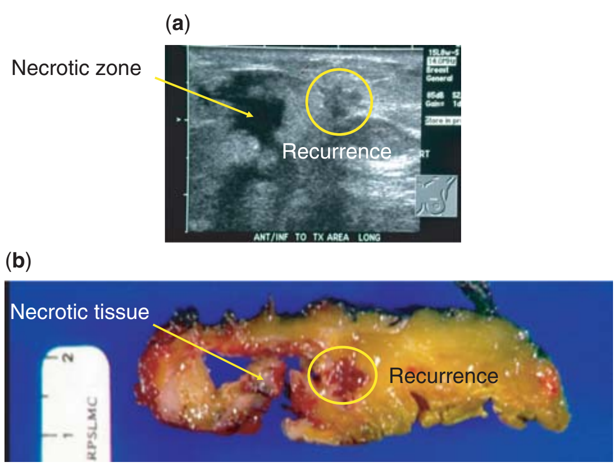

Figure 14.
*The surgically excised tumor (**b**) matched in size and shape with the US image (**a**) as shown above.*

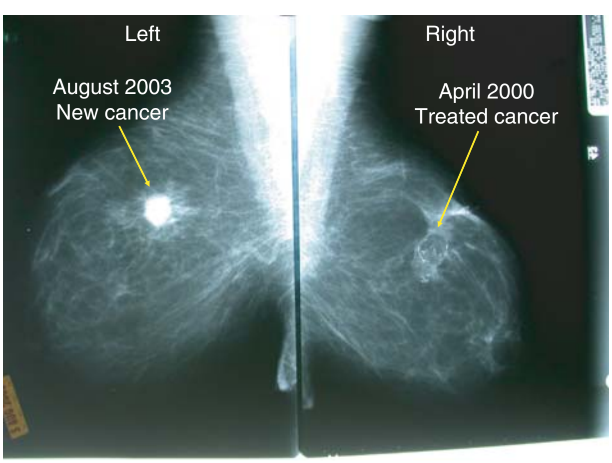

Figure 15.
Case No. 3: Annual mammogram showing the fibrotic area in the right breast where the previous tumor was ablated and the presence of a new cancer in the contra-lateral breast.

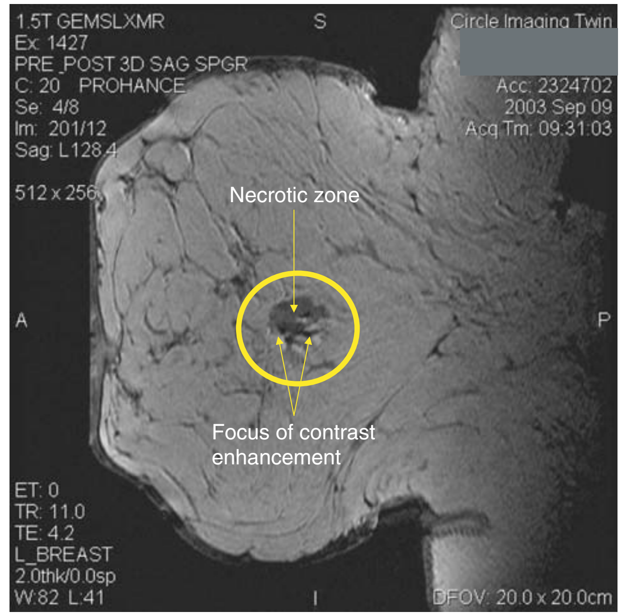

Figure 16.
MRI, coronal section of laser treated breast cancer showing a focus of contrast enhancement suggestive of residual malignancy.

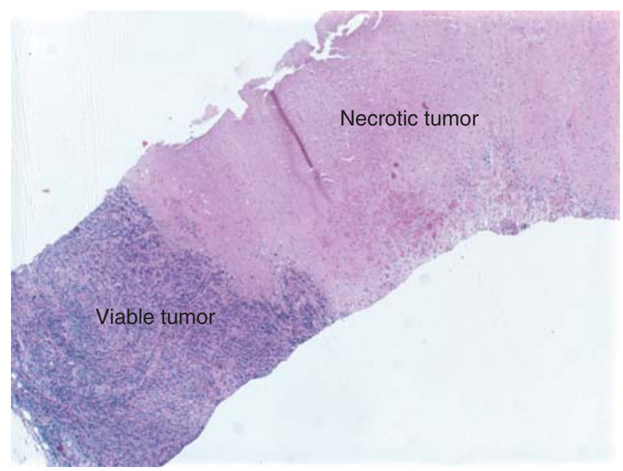

Figure 17.
Image-guided needle core biopsy confirming residual cancer.

to the development of an alternative treatment to lumpectomy for of a subset of small breast cancers. Our current surgical management of breast cancer is not in line with advanced imaging technology. Lumpectomy is an operation designed for surgical removal of a palpable breast mass. The screen detected (by mammogram or MRI) in-situ and invasive breast cancer is beyond the tactile appreciation, even at times, intra-operatively. In an attempt to remove the entire cancerous tissue the surgeon excises a segment of marked (wire-localized) breast tissue. This is a 'sledge hammer for fly' approach for treatment and should be replaced with an image-directed technique, as was the case for diagnosis of

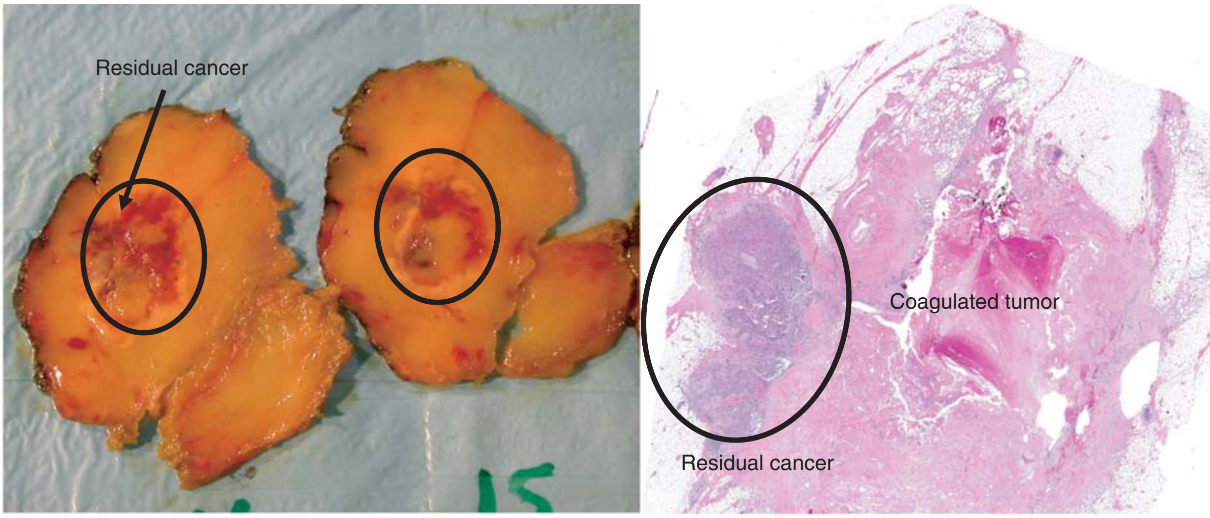

Figure 18.
Serial 3 mm sections of the laser treated breast cancer revealing a 5 × 7 × 9 mm bi-lobed residual carcinoma matching the MRI image.

mammographically detected breast cancers two decades ago. Obviously this technique is at its infancy and has to be tested in a prospective randomized multi-center trial before it can be adopted for routine application.

Second, to report that the determination of the tumor size and the margin clearance as well as the monitoring of the laser treated breast cancers may also be made through the application of the available imaging techniques. These issues are briefly addressed.

Tumor size

Good correlation between sonographic and pathologic breast tumor size have been reported [9,10]. Finlayson and MacDermott [11] reported that the mean difference between US and pathologic size of invasive ductal carcinoma was 0.33 cm ($P = 0.008$). The exceptions are invasive lobular and extensive ductal carcinoma in situ (DCIS). With the emergence of three-dimensional US, it is anticipated that the image-tissue correlation of breast cancers will be determined more accurately. It should also be noted that the conventional means of measuring the tumor size by the pathologist is fraught with some variation such as tissue shrinkage post-resection, plane of bisection, etc. In this report, cases 2 and 3 demonstrate the close image-tissue correlation. Both US and MRI tumor measurements were within 1–2 mm of the pathology numbers.

Margin clearance

Up to 22% of lumpectomies for breast carcinoma have been reported with positive resection margins [12]. In an elegant and comprehensive review of the subject, Singletary reported that it was the gross presence of the malignant cells and not the width of the clear margin which dictated the risk of local recurrence. Thus the margin width of 1 mm vs. 2–3 mm vs. 10 mm does not appear to influence the rate of local recurrence of 3–5% in 5 years [13]. With an average size differential of 3.3 mm between image and pathology [11], one could treat tumors of up to 10 mm with ILT which creates a 25 mm. zone of necrosis around the tumor or 7.5 mm coagulation all around the 10 mm tumor. The extra 4.2 mm will compensate for any 'off-center' placement of the laser needle in the targeted tumor. Case No. 1 in this report illustrates this point. The recurrence of carcinoma in Case No. 2 after 30 months may be related to the indolent nature of this disease, which locally persists in some individuals and should be handled less invasively.

Surveillance

Case No. 3 illustrates our ability to detect residual cancer at the periphery of the necrotic zone by MRI; and case 2 provides evidence that recurrence can be detected at a very early stage by high resolution US. More sophisticated imaging techniques for detection of residual or recurrent cancer are also appearing on the horizon. Whereas the routine MRI relies on the increased vascularity of the tumor, the MR spectroscopy (MRS) relies on the higher metabolic rate of the malignant tumors. Proton MRS (^{1}HMRS) of the breast has been shown to differentiate malignant from benign tumors and to be an effective tool in demonstrating the tumor response to neo-adjuvant therapy. Thus the signal change in the choline metabolism of the tumor from high to low, is indicative of its

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ablation by a destructive agent either drugs or laser. Currently the target to noise signal is not sensitive enough for detection of microscopic residual cancer at the margin of the laser treated tumor but technological improvement is anticipated in this field [14].

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