

MINIMALLY INVASIVE TREATMENT OF BREAST CANCER

ILIJA GUTEŠA, TOMISLAV OREŠIĆ, DOMAGOJ ELJUGA, IVAN MILAS,
MLADEN STANEC and DANKO VELIMIR VRDOLJAK

Department of Surgical Oncology, University Hospital for Tumors,
University Hospital Center Sestre milosrdnice, Zagreb, Croatia

Summary

The development of diagnostic methods and screening leads to early detection of breast cancer, which is why aspirations are moving towards more conservative local treatment methods. New, non invasive and minimally invasive methods, should attain same local control, with less cosmetic defects, side effects and complications compared to standard surgery. Five methods are being researched in clinical trials: cryoablation, radiofrequency ablation, laser ablation, microwave ablation and ablation by focused high intensity ultrasound waves. Although some results are promising, these methods need further technical development and prospective comparison with today's golden standard - oncoplastic breast surgery.

KEY WORDS: *cryoablation, radiofrequency ablation, laser, microwave ablation, focused ultrasound*

MINIMALNO INVAZIVNO LIJEČENJE RAKA DOJKE

Sažetak

Razvojem dijagnostičkih mogućnosti, i probira karcinom dojke se otkriva u sve ranijem stadiju, zbog čega se teži sve poštenijim metodama lokalnog liječenja tumora. Nove, neinvazivne i minimalno invazivne metode trebale bi pružiti jednaku lokalnu kontrolu, ali uz manje kozmetičke defekte, nuspojave i komplikacije u odnosu na kirurške zahvate. Trenutno je u istraživanju pet metoda: krioablacija, radiofrekvencijska ablacija, laserska ablacija, mikrovalna ablacija i ablacija fokusiranim ultrazvučnim valovima. Neke od navedenih metoda pokazuju ohrabrujuće rezultate, ali zahtijevaju dodatno tehničko usavršavanje i prospektivnu usporedbu s današnjim zlatnim standardom - onkoplastičnim kirurškim zahvatima.

KLJUČNE RIJEČI: *krioablacija, radiofrekventna ablacija, laser, mikrovalna ablacija, fokusirani ultrazvuk*

INTRODUCTION

With development of diagnostic methods and screening, breast cancer is detected at an earlier stage, which is why aspirations in breast cancer treatment are moving towards more conservative methods. New, minimally invasive methods, which would attain local control of breast conserving surgery, while reducing the frequency and severity of complications, are being researched. The goal of these methods is to create less cosmetic defects, less pain, and deliver faster patient recovery

and lower treatment costs. In minimally invasive procedures, tumor tissue is destroyed by heating or freezing. Five methods are currently being researched in clinical trials: cryoablation, radiofrequency ablation, laser ablation, microwave ablation and ablation by focused high intensity ultrasound waves. The first four methods are invasive and the ultrasound method is noninvasive. Ablation techniques vary in their technical characteristics, as well as applicability in clinical practice, and are thus considered methods which are still in research.

EXAMINATION

Before choosing a noninvasive treatment of breast cancer, a detailed imaging estimating the extent of the tumor needs to be provided, as well as the position of the tumor in relation to the skin, pectoral muscle and heart. Extensive intraductal component and lobular invasive carcinoma need to be ruled out first. Also, core needle biopsy should be done to obtain the necessary histology and immunohistochemistry data.

Since the ablation procedure can disrupt the lymphatic drainage of the breast, the sentinel lymph node (SLN) status needs to be determined prior to ablation. After ablation, it is necessary to perform a magnetic resonance imaging (MRI) to assess tumor destruction. Ablations which require MRI or ultrasound guidance need to be done by a physician with extensive experience in stereotactic needle biopsy.

CRYOABLATION

Cryoablation efficiency in complete tumor ablation is between 36 and 93% (1-4). The best results are achieved in treatment of tumors smaller than 1.5 cm (3,4). Patients with tumors larger than 2 cm are considered bad candidates for this type of treatment due to the presence of tumor extension which is not visible by ultrasound. Cryoablation can be used as a definitive form of treatment of large tumors and higher grade tumor in elderly patients with unresectable breast cancer and in patients who refuse surgery, without recurrence within 18 months (5,6). The procedure is usually performed by placing a 3-millimeter probe in the geometrical center of the tumor under ultrasound control (7). The necrosis is achieved by freezing the tumor tissue and anoxia-induced damage to the tumor blood vessels. The procedure lasts for about 30 – 40 minutes in total. Freezing (-40 to -160°C) is achieved by rapid expansion of argon gas or liquid nitrogen, which creates a 4-7 cm large ice ball. A discrete hyperechoic ring visible by ultrasound marks the boundary of frozen and non-frozen tissue. Margin of 1 cm around the tumor is necessary in order to achieve complete cell death. To prevent damage to the skin, saline should be injected between the skin and the ice ball during the procedure, especially if a distance between the ice ball

and the skin is less than 5 mm. This kind of protection enables ablation of tumors close to the skin, which is not possible with ablation methods based on high temperature (8,9). The ice ball is melted passively or actively using helium, after which the probe is removed from the ball. Due to analgesic effect of ice, it is possible to perform the procedure under local anesthesia, which is a significant advantage compared to high temperature based ablations which usually require general anesthesia or intravenous sedation.

The only reported complication with cryoablation is skin necrosis, which is a result of insufficient distance between the ice ball and the skin. There have been no reported complications of damage to the pectoral muscle or chest wall. The histologic image of surgically removed tissue after 2-4 weeks shows absence of tumor cells, and presence of inflammatory cells and fat necrosis (8).

Cryoablation is not recommended for in situ carcinoma or for lobular invasive carcinoma due to difficult ultrasound assessment of local extent of the disease.

Today, the method can be routinely used to remove fibroadenomas, with excellent cosmetic results, minimal complications (10) and high level of patient satisfaction. After the procedure a breast MRI should be performed to identify potential residual disease. The presence of so called cryohalo indicates successful cryoablation and negative edges (11). The latest cryoablation clinical study conducted on 15 women with tumors 4 – 12 mm in diameter has shown the accuracy of MRI in detection of a solitary case of a 3 mm residual disease, which is considered caused by the suboptimal probe position during the procedure (1).

The efficacy of cryoablation, pre-intervention and post-intervention MRI is currently being researched in the multi-center clinical trial Z1072 (12).

Animal models have shown antitumor immunity after thermoablation techniques. It is assumed that the tumor-specific immune response caused by antigens from the damaged cells may contribute to control of the distant metastases (13). In some cases, complete tumor regression was observed (14). Unlike high temperature based ablation methods, cryoablation does not cause coagulatory necrosis, thus allowing massive antigen presentation in the presence of proinflammatory cytokines. Increased lymphocyte toxicity and acti-

vation of NK cells was demonstrated in animal models, the activity of which is reduced in conventional surgical procedures. The effect of cryoablation stimulated anti-tumor immune response on recurrence and metastasis is also being examined in the clinical trial Z1072.

RADIOFREQUENCY ABLATION

In radiofrequency ablation (RFA), a metal electrode is inserted into the breast, which is connected to a radiofrequency generator of 200 W and 400 – 800 kHz (15-20). The electrode induces a current which heats the surrounding tissue due to ion agitation (21). With heating the conductivity of the tissue reduces, which limits the ablation range. A grounding pad is placed on the skin to direct the current from the tissue which is further away from the electrode. Active cooling helps in achieving larger ablation zones. The placing of electrode can be guided by ultrasound or MRI. Nowadays, MRI compatible electrodes are available. Using modern, multi-shaft electrodes allows for ablation of greater tissue volume (3 – 6 cm) in the duration of 10 – 15 minutes. However, due to changes in tissue conductivity during heating, the ablation zone can be inhomogeneous and if there is no image control during the procedure the results of the procedure may be unpredictable.

Initial feasibility studies have shown 76 – 100 % efficiency of RFA in complete tumor ablation (22). Due to difficulties in inserting multi-shaft electrodes into solid and fibrous tissue, the need to use more single-shaft electrodes with the aim to encompass larger tissue volumes is being considered. However, this increases the cost and duration of the procedure. As with other heat based ablation techniques, the pain of the procedure represents a problem.

MICROWAVE ABLATION

Microwave ablation is based on electromagnetic heating of water-rich tissue by using waves with the frequency from 900MHz to 2450MHz. Two methods, which have shown different results, are being tested. In *focused microwave therapy* the probe is placed in the center of the tumor, usually with ultrasound control. Patients are in a prone position with compressed breast, and the process

lasts for about 60 minutes. The probe focuses microwaves and monitors the field amplitude during the procedure. A temperature probe is also placed in the tumor, and a cooling system is used to protect the skin. This method provides heterogeneous tumor necrosis, and complete ablation was achieved only in 0 – 8 % of the cases (22,23). A recent clinical trial demonstrated the efficacy of this method in reduction positive surgical margins and a significant tumor reduction in combination with neoadjuvant chemotherapy (24). Complications include severe pain and skin burns as well as discomfort during prolonged prone position.

Percutaneous microwave coagulation showed a 90 % success rate in ablation of tumors smaller than 3 centimeters (25). This method is done by 2450MHz frequency waves with a needle antenna in the center of the tumor. Incomplete ablations were explained by inadequate needle positioning and inaccurate pre-intervention assessment of tumor extent. The procedure is performed under ultrasound control, and the tumor becomes echogenic and disappears in under 10 minutes. Downsides of this method are the need for general anesthesia and reported complications such as skin burns and damage to the large pectoral muscle.

FOCUSED ULTRASOUND SURGERY

Ultrasonic energy can be used for ablation by using interstitial applicators or extracorporeal conduction into the body (21, 26-29). Extracorporeal ablation techniques are most often described using names such as Focused Ultrasound Surgery (FUS) and High Intensity Focused Ultrasound (HIFU). These systems use air-based conductors which are acoustically connected to the patient. Power of 100 W with a frequency of 1-2 MHz is used for energy transfer to the target in the breast. In current systems there is spatial restriction of energy transfer, which is why multiple applications are necessary for ablation of larger tumors. Systems which would enable faster ablation of larger tumors are currently being researched. Diagnostic imaging methods are used in planning and targeting of tumors, and ultrasound and magnetic resonance imaging are currently being tested.

Although ultrasound has the advantage of simplicity, speed and low cost, MRI is better at

showing soft tissue contrast and has the option to visualize and quantify focal warming.

The patient lies on her stomach and is acoustically connected to the system (30). Cooling systems are used to protect the skin. The patients are usually continuously intravenously sedated. MRI T1-W images with contrast are used for visualization and procedure planning. Due to possible damage to the skin and pectoral muscle, careful selection of suitably located tumors is necessary. MRI thermal imaging (MRTI) is used to visualize heating of the lesions during procedure (31). Low energy pulses can periodically be used to localize the ray. The ablation procedure is performed using high energy pulses for 10 – 30 seconds for ablation of volume units 1-5 mm in diameter and 0.5 – 3 cm in length. The ray is moved mechanically and electronically to achieve conformal delivery of multiple sonications to the targeted tissue. The temperature of targeted tissue is increased to 50 – 90°C, with very sharp transition between treated and untreated tissue. Multiple sonications and necessary pauses between sonications result in a 45-120 minutes procedure for tumors up to 2 cm in diameter.

For now, there are very few studies which evaluate the use of FUS in breast tumors. The first feasibility studies show different rates of complete ablation (24% - 100%) (32). In addition to patient selection, the use of this method is limited by the duration and pain of the procedure. Direct injection of anesthetic into the targeted area is controversial because the ultrasound ray may affect the injected substance, as well as cause significant harm to the skin at the injection point.

LASER ABLATION

Laser ablation is performed by delivering high energy light (800 – 1065nm) into the tissue using an applicator (33-35). The light absorbs in the tissue around the laser, which leads to intense heating of the tissue around the applicator (21). Cooling the laser catheter prevents tissue carbonization in contact with the catheter, which allows for use of higher power lasers for ablation of larger tumors. Class IV lasers are used for ablation, which requires adequate education, equipment and official registration of the user.

Ultrasound or MRI guidance can be used for navigation. Since there are no metal components,

morphological and functional MRI imaging can be used without major artifacts. As in focused ultrasound ablation, MRTI can be used for localization and monitoring the laser treatment. The size and strength of ablation depends on the wave length, power, applicator cooling and local perfusion. Due to these factors, ablation can last from 90 seconds to several minutes, and the lesion size can also vary from 1.5 to several centimeters. The ablation zone is ellipsoidal, located centrally around the applicator.

The initial feasibility studies show 13 – 91% laser efficiency in complete tumor ablation (32). The ablation width is slightly less on average than those of RFA and microwave ablation, which is why more applications are necessary for larger ablations, which extends the duration of the procedure and increases costs. As with RFA, microwave ablation and FUS, pain caused by the procedure is a problem.

CONCLUSION

Most clinical trials on breast cancer ablation were conducted on cryoablation procedures and RFA in second phase studies. The results show that the effectiveness of complete ablation for RFA is 76% - 100%, for cryoablation 36% - 93%, and for ultrasound ablation 20% - 100%. RFA requires local analgesia, sedation or even general anesthesia, while thermal-based methods show significant incidence of burns, pain and patient discomfort. The advantages of cryoablation are simplicity, low equipment cost, high level of patient comfort, safety in ambulatory conditions, as well as the growing number of clinical trials. Great hopes are placed in the potential effect of ablation techniques, especially cryoablation in increasing tumor-specific immunity which could contribute to control of distant metastases.

In conclusion, the development of new methods for local breast cancer treatment should be encouraged and accepted, but with a high dose of criticality with the aim of providing the best possible patient care. Before introducing new methods to standard clinical application, it is necessary to prospectively evaluate the short- and long-term complications, such as burns, chest wall injuries, seroma, hematoma, cosmetic defects and, most importantly, incidence of local recurrence of the

disease. It is important to keep in mind that for every four local recurrences avoided at five years, one death from breast cancer is prevented at 15 years (36).

Also, it is important to assess patient satisfaction, especially when compared to oncoplastic surgical procedures which show satisfactory cosmetic results and represent the standard in today's surgical treatment of breast cancer.

REFERENCES

- Manenti G, Perretta T, Gaspari E, et al: Percutaneous local ablation of unifocal subclinical breast cancer: Clinical experience and preliminary results of cryotherapy. *Eur Radiol.* 2011;21:2344-2353.
- Zhao Z, Wu F: Minimally-invasive thermal ablation of early-stage breast cancer: A systemic review. *Eur J Surg Oncol.* 2010;36:1149-1155.
- Pfleiderer SO, Freesmeyer MG, Marx C, et al: Cryotherapy of breast cancer under ultrasound guidance: Initial results and limitations. *Eur Radiol.* 2002;12:3009-3014.
- Sabel MS, Kaufman CS, Whitworth P, et al: Cryoablation of early-stage breast cancer: Work-in-progress report of a multi-institutional trial. *Ann Surg Oncol.* 2004;11:542-549.
- Littrup PJ, Jallad B, Chandiwala-Mody P, et al: Cryotherapy for breast cancer: A feasibility study without excision. *J Vasc Interv Radiol.* 2009;20:1329-1341.
- Tanaka S: Cryosurgical treatment of advanced breast cancer. *Skin Cancer.* 1995;10:9-18.
- Tozaki M, Fukuma E, Suzuki T, et al: Ultrasound-guided cryoablation of invasive ductal carcinoma inside the MR room. *Magn Reson Med Sci.* 2010;9:31-36.
- Roubidoux MA, Sabel MS, Bailey JE, et al: Small (<2.0 cm) breast cancers: Mammographic and US findings at US-guided cryoablation - initial experience. *Radiology.* 2004;233:857-867.
- Sabel MS: Cryo-immunology: A review of the literature and proposed mechanisms for stimulatory versus suppressive immune responses. *Cryobiology.* 2009;58:1-11.
- Littrup PJ, Freeman-Gibb L, Andea A, et al: Cryotherapy for breast fibroadenomas. *Radiology.* 2005;234:63-72.
- Levine G, Poplack S, Barth R, et al: New findings on contrast-enhanced magnetic resonance imaging (CEMRI), the "Black Hole" and "Cryohalo" are markers for the efficacy of ultrasound (US)- guided cryoablation of small (r15 mm) unifocal invasive ductal breast cancer (IDC). *RSNA2008: 94th Scientific Assembly and Annual Meeting of the Radiological Society of North America, 2008: SST01-05.* <http://archive.rsna.org/2008/6012933.html> accessed on 02.09.2015.
- Simmons, R. The American Society of Breast Surgeons. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. <https://www.breastsurgeons.org/docs2014/press/Cryoablation%20-%20Simmons%20-%20ASBrS%2014%20Press%20Release.pdf> accessed on 02.09.2015.
- Haen SP, Pereira PL, Salih HR, et al: More than just tumor destruction: Immunomodulation by thermal ablation of cancer. *Clin Dev Immunol.* 2011;2011:160250.
- Suzuki Y: Cryosurgical treatment of advanced breast cancer and cryoimmunological responses. *Skin Cancer.* 1995;10:19-26.
- Vilar VS, Goldman SM, Ricci MD, et al: Analysis by MRI of residual tumor after radiofrequency ablation for early stage breast cancer. *Am J Roentgenol.* 2012;198:W285-W291.
- Ohtani S, Kochi M, Ito M, et al: Radiofrequency ablation of early breast cancer followed by delayed surgical resection - a promising alternative to breast-conserving surgery. *Breast.* 2011;20:431-436.
- Tsuda H, Seki K, Hasebe T, et al: A histopathological study for evaluation of therapeutic effects of radiofrequency ablation in patients with breast cancer. *Breast Cancer.* 2011;18:24-32.
- Noguchi M: Radiofrequency ablation therapy for small breast cancer. *Semin Ultrasound CT MR.* 2009;30:105-112.
- Fornage BD, Sneige N, Ross MI, et al: Small (< or = 2-cm) breast cancer treated with US-guided radiofrequency ablation: Feasibility study. *Radiology.* 2004;231:215-224.
- Grotenhuis BA, Vrijland WW, Klem TM: Radiofrequency ablation for early-stage breast cancer: Treatment outcomes and practical considerations. *Eur J Surg Oncol.* 2013;39:1317-1324.
- Ahmed M, Brace CL, Lee FT Jr., et al: Principles of and advances in percutaneous ablation. *Radiology.* 2011;258:351-369.
- Gardner RA, Vargas HI, Block JB, et al: Focused microwave phased array thermotherapy for primary breast cancer. *Ann Surg Oncol.* 2002;9:326-332.
- Vargas HI, Dooley WC, Gardner RA, et al: Focused microwave phased array thermotherapy for ablation of early-stage breast cancer: Results of thermal dose escalation. *Ann Surg Oncol.* 2004;11:139-146.
- Dooley WC, Vargas HI, Fenn AJ, et al: Focused microwave thermotherapy for preoperative treatment of invasive breast cancer: A review of clinical studies. *Ann Surg Oncol.* 2010;17:1076-1093.
- Zhou W, Zha X, Liu X, et al: US-guided percutaneous microwave coagulation of small breast cancers: A clinical study. *Radiology.* 2012;263:364-373.
- Tempany CM, McDannold NJ, Hynynen K, et al: Focused ultra- sound surgery in oncology: Overview and principles. *Radiology.* 2011;259:39-56.

27. Brenin DR: Focused ultrasound ablation for the treatment of breast cancer. *Ann Surg Oncol.* 2011;18: 3088-3094.
28. Huber PE, Jenne JW, Rastert R, et al: A new noninvasive approach in breast cancer therapy using magnetic resonance imaging-guided focused ultrasound surgery. *Cancer Res.* 2001;61:8441-8447.
29. Furusawa H, Namba K, Thomsen S, et al: Magnetic resonance-guided focused ultrasound surgery of breast cancer: Reliability and effectiveness. *J Am Coll-Surg.* 2006;203:54-63.
30. Gianfelice D, Khiat A, Amara M, et al: MR imaging-guided focused US ablation of breast cancer: Histopathologic assessment of effectiveness - initial experience. *Radiology.* 2003;227:849-855.
31. Rieke V, Butts Pauly K: MR thermometry. *J Magn Reson Imaging.* 2008;27:376-390.
32. Zhao Z, Wu F: Minimally-invasive thermal ablation of early-stage breast cancer: A systemic review. *Eur J Surg Oncol.* 2010;36:1149-1155.
33. Mumtaz H, Hall-Craggs MA, Wotherspoon A, et al: Laser therapy for breast cancer: MR imaging and histopathologic correlation. *Radiology.* 1996;200:651-658.
34. van Esser S, Stapper G, van Diest PJ, et al: Ultrasound-guided laser-induced thermal therapy for small palpable invasive breast carcinomas: A feasibility study. *Ann Surg Oncol.* 2009;16:2259-2263.
35. Dowlathshahi K, Francescatti DS, Bloom KJ: Laser therapy for small breast cancers. *Am J Surg.* 2002;184: 359-363.
36. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366:2087-106.

Author's address: Ilija Guteša, Department of Surgical Oncology, University Hospital for Tumors, University Hospital Center Sestre milosrdnice, Ilica 197, 10000 Zagreb, Croatia; e-mail: ilija.gutesa@gmail.com