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MINIMALLY INVASIVE METHODS IN BREAST CANCER TREATMENT: A PROTOCOL OVERVIEW

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Summary

One can find an increasing number of articles with minimally invasive methods in current literature concerning local treatment of breast cancer. The methods can be divided in two groups: percutaneous excision methods and thermal ablation methods. Thermal ablation methods are based on the premise that malignant tissue is more sensitive to hyperthermia than normal cells.

We are comparing advantages and disadvantages of current minimally invasive methods for treatment of early stage breast cancers, showing differences and advantages over breast-conserving surgery. Available published studies and protocols are overviewed.

Most of the published works emphasize advantages over classic breast surgery such as: lower costs, less trauma for patients and smaller invasiveness. All methods involving thermal procedures require surgical excision afterwards for evaluation of necrosis and patohistological evaluation of the lesion.

The effect of these treatment methods should be safety, painlessness, good cosmetic results and lower treatment costs. If results of such methods are to be comparable to BCS, we can expect their integration in clinical practice.

KEY WORDS: *breast cancer, minimally invasive methods, percutaneous biopsy, thermal ablation*

MINIMALNO INVAZIVNE METODE U LIJEČENJU RAKA DOJKE: PREGLED PROTOKOLA

Sažetak

U suvremenom pristupu lokalnog liječenja tumora dojke sve više prostora u stručnim publikacijama zauzimaju izvješća o primjeni tzv. minimalno invazivnih metoda, među kojima su dvije osnovne skupine: perkutane ekscizijske metode i termalne ablacijske metode. Temelj termalnih ablacijskih postupaka u liječenju tumora dojke leži u činjenici da tumori pokazuju veću senzitivnost na hipertermička oštećenja od normalnih stanica.

U radu se nastoje komparacijom prednosti i nedostataka ovih suvremenih minimalno invazivnih metoda u liječenju tumora dojke nižih stadija, utvrditi razlika i eventualna prednost tih postupaka prema poštednim kirurškim zahvatima .

Pregledani su dostupni publicirani protokoli i iskustva u provođenju perkutanih bioptičkih metoda i nekih termalnih ablacijskih metoda u minimalno invazivnoj kirurgiji dojke.

U većini pregledanih publikacija i protokola, naglašena je prednost opisanih metoda nad klasičnom kirurgijom dojke, koja je izražena u nižim troškovima, smanjenju psihičkih trauma liječenih bolesnica i niskom razinom invazivnosti. U gotovo svim pregledanim protokolima koji se odnose na tzv. termalne metode uočena je potreba za naknadnom kirurškom ekscizijom radi procjene stupnja nekroze i patohistološke provjere lezije.

Uspješnost liječenja tumora dojke ovim metodama bi se trebala temeljiti na sigurnosti, bezbolnosti, dobrim kozmetičkim rezultatima i nižim troškovima liječenja. Ove bi metode mogle doživjeti punu primjenu u kliničkoj praksi ako se njima postigne rezultat ekvivalentan onome koji se postiže sa poštednim kirurškim zahvatima (BCS).

KLJUČNE RIJEČI: *tumori dojke, minimalno invazivne metode, perkutana biopsija, termalna ablacija*

INTRODUCTION

We are witnessing a question raised over and over again: Is there a place for breast cancer surgery without a scalpel?

This question should be considered in the context of increasingly smaller tumors, discovered at earlier stages due to better diagnostics, usually mammography screening. At the same time, this asks for a deviation from traditional, radical surgical procedures over breast-conserving (BCS) procedures, including procedures ranging form sentinel node biopsy (SNB) to today's minimally invasive procedures (1). The latter is offering less mutilation, less physical frustration for patients but also a decrease of procedure costs, since these procedures are usually not carried out in operating rooms (2).

The mentioned procedures require several technical conditions, a well educated staff, familiar with radiology basics, molecular biology and carefully selected patients, having in mind their tumor stage and psychological profile (3).

The basic goal of almost all minimally invasive procedures is to achieve treatment comparable to BCS.

Prior to attempting any minimally invasive method several points need to be addressed:

- What is the energy conduction of breast tissue?
- Is energy transferred percutaneously or transcutaneously to tissue?
- Does the procedure require an operating room or not?
- What are the side effects?
- How much time does it take to finish the procedure?
- How much does the procedure cost?
- What type of anesthesia is required?

Minimally invasive procedures can be classified as (4-6):

- Percutaneous excision methods (biopsies)
- Thermal ablation methods
- Chemical methods

All types of procedures emphasize required precision in tumor localization as a necessary step in determining its size and borders. Despite the fact that mammography and ultrasound (US) are used as screening and diagnostic tools, magnetic resonance imaging (MRI) is gaining momentum towards being considered the gold standard for depiction of preoperative tumors and determination of the stage of the disease (7). A limiting factor in determining the extent of invasive lobular carcinoma (LC) and ductal carcinoma *in situ* (DCIS) are characteristics of US and MR imaging (3).

Percutaneous biopsy methods

Biopsy as the commonest breast intervention is often the first intervention step towards breast cancer treatment and can be delivered as:

- Fine needle aspiration (FNA)
- Core needle biopsy (CNB)
- Advanced breast biopsy instrumentation (ABBI)
- Vacuum assisted breast biopsy (MIBB, Mamothome)

Over 90% of primary mammalian lesions can be diagnosed using FNA or CNB with local anesthesia (Vega et al. 1995, Scopa et al. 1996, O'Neil et al. 1997, Pijnappel et al. 1997, Gotzinger et al. 1998).

Also, CNB is usually a very accurate method in determining the nature of both benign and malignant breast lesions. In malignant cases, this procedure is followed by one of the BCS methods, usually a lumpectomy or segmentectomy. No further therapy is necessary in benign cases. Problems may rise if a benign, palpable lesion is a burden to the patient or the finding is atypical ductal hyperplasia (ADH) or a radial scar. These lesions need to be removed *in toto*.

Nowadays, devices used for percutaneous excision biopsy (PEB) could be divided as:

- Devices used to sample a single larger sample of tissue using one incision
- Devices used to sample several smaller samples using one incision

The ideal is to sample a maximum amount of target tissue using one incision, as small as possible. Among devices that remove one block of tissue one can use two types of devices:

- Site select stereotactic breast biopsy system, with probes of 10, 15 and 22 mm, and
- *En block* breast biopsy system, with probes of 10 and 15 mm.

The advantage of such biopsy procedure is that the surgeon is able to remove the complete lesion if it is precisely localized, sparing the surrounding tissue during the procedure. It is not necessary to use the operating room and therefore, the procedure costs less. Finally, if the finding is atypical ducal hyperplasia (ADH) or radial scar, the physician can still mark the lesion with the wire and then send the patient for surgical excision.

Several protocols mention the following devices for taking multiple samples:

- Mammotome breast biopsy system (vacuum-assisted biopsy)
- Minimally invasive breast biopsy/Automated tissue excision and collection (MIBB/ATEC)

Both systems use vacuum to assist tissue extraction with rotating blades without removal of the core biopsy needle from the breast and the incision site is only 5mm long thus no stitching is necessary. MIBB apparatus can use two types of chambers for reception of samples (10 and 20 mm), while Mammotome uses a 19mm long chamber (3). Published data on usage of ATEC are scarce (8), compared to Mammotome, which is considered today as instrument of choice, especially in cases of non-palpable lesions with micro calcifications that can be removed *in toto* (9).

One multicentric study (10) used US-guided mammotome on 124 patients with lesions up to 30 mm in diameter. While reporting insignificant side effects, 97% of patients were satisfied with the resulting scar, while the lesion was not palpable in 98% of cases. Finally, 92% patients would recommend this procedure to other patients!

After sampling, a Micro Mark Clip is placed, marking the site and the path of biopsy. On the other hand, the MIBB system uses an exteriorly placed rotating knife and gains up to 25% more tissue. This method implies high diagnostic accuracy, lower expense, low morbidity and high acceptance rate among both patients and surgeons (11, 12).

The main advantages of both VAB systems are: micro calcification removal (Leberman 1997, Meyer 1997), sample is large enough, made with single insertion (Simon 200), and up to 50% lower price, compared to surgical open biopsy (13).

On the other hand questions are raised about shortcomings of VAB:

- Is the whole lesion removed?
- What is the status of the edge of tumor?
- Reconstruction of histological architecture of tumor?

Following patients are not suitable for VAB:

- Lesion close to the skin surface or deep, near to *m. pectoralis fascia*
- Persons that cannot be still on their back for 20-30'
- If using anticoagulants or with similar disorders
- Not cooperative or mentally ill/challenged patients
- Allergic to medication given during procedure
- Patients with cardio respiratory failure
- Arthritis patients

Advanced breast biopsy instrumentation (ABBI system)

This procedure provides about 50% of tissue usually acquired with open surgical biopsy and marcation needle, which is still more than the core biopsy mentioned above. It was developed as an alternative to excision biopsy for non-palpable tumors. A surgical cannula is inserted through axial guide and a tissue sample, cylindrical in shape, is taken.

The system does not require multiple skin penetrations and does provide enough edge of tumor for better histological analysis. Specificity and sensitivity are excellent.

The percentage of positive edges and the residual tumor is comparable to excision biopsy with marcation wire. (Velanovich et al. 1999). The procedure does not require an operating room, thus lowering costs comparing to surgical biopsy. This technique has been tested in several institutions with good results (Sheth 1999, Portincasa 2000, Schwartberg 2000).

A drawback of ABBI is the 2 cm wide skin incision needed for the cannula.

Thermal ablation methods

The minimally invasive thermal ablation procedures are:

- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- High-intensity focused ultrasound (HIFU)
- Interstitial laser thermal ablation (ILTA)
- Cryoablation (CA)

Radio frequency ablation

RFA is based on thermo effects of high frequency electrical current sent directly to the tumor, causing hyperthermia and thus killing the cells. Changes in the cell wall permeability and disruption of electrolytic balance destroys the cell along side with coagulation that damages vital parts of the cell and DNA.

These changes are starting at temperatures above 41 degrees Celsius (315 degrees Kelvin) and cell death is observed if temperature rises above 42.5 degrees Celsius (15). Some publications advocate raising the temperature as high as possible (16), but with carbonification of tissue as a side effect.

Published articles report usage of RFA with tumors of liver, bones, prostate and brain, with different results (14, 17). Jeffrey et al. (18) was among first to apply RFA on breast tumors.

The first published work reports only five patients with intraductal carcinoma, 5 cm in diameter, clinical stages III and IV. The mentioned authors pointed out that RFA is more effective on small lesions, up to 3 cm in diameter. Despite recommendations for RFA not to be used in operating rooms, this procedure is still carried out in them, where the procedure can be converted to surgical resection. The procedure is carried out with strong sedation or even general anesthesia. Histological examination of treated tissue is carried out using staining with reduced nicotine amide dinucleotide (NADH) and hematoxiline-eosine (H/E) staining to assess damage inflicted on tumor cells.

So-called RITA probes have different number of heat-inducing wires, placed in several points inside the lesion. In breast lesions RFA probe is positioned under supervision of real-time US or using stereotactic guidance (16). Bleeding during this procedure is smaller compared to RFA of the liver or brain lesions; therefore, the heat dispersion in surrounding tissue is smaller ("heat sink"), too. Patients are irradiated after RFA, similar to patients treated with lumpectomy. Some RFA protocols exclude patients with multicentric or multifocal tumors (19) therefore avoiding surgical excision following RFA.

With more treated patients, problems with this method become more apparent. Since breast contains considerable amounts of fat tissue, which has got low conductivity, duration of procedure sometimes needs to be enlarged. Heterogeneity of tissue also affects impedance, changing the needed time for this procedure. Having all that in mind, RFA is, for now, limited to small tumors.

Minimal conditions for RFA are:

- Invasive lesion smaller than 2cm.
- Distance between thorax wall or skin and tumor larger than 1cm
- Intact skin
- Clear depiction of lesion on US (symmetric and with clear borders)

Protocols overview:

Publications show RFA as a useful method in liver tumors (resectable ones), and promising results have been shown in lung, bone, brain and pancreas tumors (14). This method was also used on renal and adrenal lesions with variable results

Table 1.

RADIOFREQUENCY ABLATION: EXPERIENCE AND PROTOCOLS

Protocol:	Patients	Tumor size	Complete ablation	Incomplete ablation	Complications	Report year
Jeffrey et al.	5	T_2-T_3	4 (80%)	1	0	1999.
Jzzo et al.	26	T_1-T_2	25 (96%)	1	Skin Burn (1)	2001.
Elliott et al.	1	T_1	1 (100%)	0	0	2002.
Burak et al.	10	T_1	9 (90%)	1	0	2002.
Noguchi et al.	2	T_1	1 (50%)	1	0	2003.
Fujimoto et al.	9	T_3-T_4	7 (78%)	2	0	2003.
Singletary et al.	29	T_1	25 (86%)	2	Skin burn(1)	2003.

Modified from: Noguchi M. Minimally invasive surgery for small breast cancer, J Surg Oncol 2003; 84: 94-101

(20). After first results from Jeffrey et al. (18), Izzo et al. (21) published their results in 26 cases with intraductal tumors of stage I and II, smaller than 3cm in diameter.

E. Singletary described 29 patients with tumors up to 2 cm (22). In 25 out of 29 patients complete ablation was achieved. It is believed that poor outcome in 4 patients was caused by inaccurate determination of size and shape of lesions. One patient had skin necrosis. Hayashi et al. treated 22 patients with lesions smaller than 3cm in diameter and the ablated area was 5mm wider than the lesion (23). Vital tumor cells were found inside the resected tumor tissue in 8 out of patients. The main reason for such result was believed to be multifocality and eccentric shape of lesions, which was not recognized before the procedure.

Pathological and US findings concurred in 75% cases. Recurrance of the disease was recorded at the same level as in patients treated with lumpectomy, indicating that transfer of electrical current was strongly affected by fat tissue of the breast. Further studies are necessary to assess long-term results of this method.

Technical problems of RFA

High increase of temperature around the probe changes impedance of the tissue exponentially, and can lead to carbonization of the surrounding tissue, making RFA suitable for smaller lesions. Finally, in cases where RFA is the only usable method, the cosmetic result is still not clear.

This method has got unwanted effects, such as: skin or pectoral muscle damage (if lesion is within 1 cm from them), and unknown time of resorption of treated tissue (lump can still be palpable moths after).

A recent study (25) reports MRI as a very efficient tool for monitoring of RFA, when MRI can be used. The drawback of MRI is smaller specificity (26) and poorer detection of ductal *in situ* carcinoma (DCIS) and lobular carcinoma (LC)(27).

White coagulated tissue is clearly visible in resected tissue, surrounded with 5 mm wide ring of red colored tissue. In tumors up to 1 cm in diameter, complete eradication of tumor cells is possible, with 1 cm wide zone of surrounding tissue. While some protocols predict that further irradiation is necessary, we were unable to find information considering long-term changes of ablation field, but *in toto* resorption is likely.

The future of RFA of primary breast cancer should give results comparable to BCS, a method considered to be a standard for treatment of small breast tumors. So far, RFA pilot studies include excision and PH evaluation of ablated tissue (8), making RFA more expensive than surgery alone, for now. The next logical step is making RFA stand-alone method, since RFA is also mentioned as replacement of neoadjuvant therapy of breast cancer in advanced stages (28).

Microwave ablation (MWA)

Despite the fact that microwave technology has been available for decades, we have seen a negative trend of using MWA in medicine due to surrounding tissue damage. Hyperthermia induced with microwaves has been documented as effective against several cancers ad as adjuvant to chemotherapy and irradiation (29). As in other hyperthermal methods, the goal is to raise temperature of neoplastic tissue above 45 degrees Celsius and cause necrosis (30).

Old devices were unable to penetrate tissue deep enough and higher energy used more extensive damage to healthy tissue including skin. Recently developed devices have phase adaptable probes, enabling treating deeper layers of breast, while avoiding skin damage by focusing energy in deeper layers of the breast.

Gardner et al. published a study with tumors from 1 to 8 cm in diameter (31). Temperature of the skin was monitored and surface of the breast was cooled with fan. In this study, skin temperature was kept under 42.5 degrees Celsius. All patients had subsequent surgery where residual tumor was evaluated and the extent of necrosis was evaluated histologically. Average duration of treatment was 35 minutes. Some studies suggest that heating tumor tissue above 49.7 deg. Celsius yields more destroyed tumor cells (32). Similar to other hyperthermic methods, further studies are needed.

High intensity focused ultrasound

Theoretical basis of HIFU was made back in 1962 (33). During this procedure target tissue is heated at up to 90 deg. Celsius within 10 seconds (34).

Energy is transferred from probe to tissue using a thin layer of gel, similar to diagnostic ultrasound. Focused ultrasound penetrates tissue and,

causing hyperthermia, destroys the cells on a small area, 5 to 10 mm in diameter. It is considered that both heat and cavitation causes necrosis (35).

But, as mentioned before, the heterogeneity of most tumors and their position close to the skin made HIFU impractical in many types of tumors. On the other hand breast tumors are more accessible, without bones or air close by, making HIFU more possible.

MRI combined with HIFU was first mentioned by Huber et al. (36), where MR is used for localization, tracking and monitoring of HIFU application within about 2 cm wide tumor. Five day later, the lesion was removed and HIFU was within 1-2 mm of desired coordinates.

The Anderson Cancer Center, Texas, carries a study with magnet-focused ultrasound in an attempt to treat early breast cancer (smaller than 2 cm). After treatment, treated tissue was removed, necrosis evaluated and compared to both preoperative MRI and residual tumor in removed tissue (3).

HIFU as therapeutic method needs clinical trials (37), but due to complex technical setup, it will most likely be reserved for larger institutions (30).

Interstitial laser thermal ablation (ILTA)

The first application of laser dates back to 1960s when it was used as a palliative tool for urinary, gastrointestinal and bronchial tumors. Obstructed bronchus and esophagus was successfully treated by evaporating tumor tissue using high-power laser (38). ILTA is mentioned as a therapeutic method for the first time in 1983. Necrosis by causing hyperthermia is achieved after high laser emits light through a fiber optical probe to target tissue. Resorption and reparative fibrosis follow (8). In some cases surgical excision is not necessary.

One protocol (39) was used on 36 patients using a laser probe size 16-18 G while on stereotactic table. Treatment duration was 20 minutes. Afterwards, within 1-8 weeks standard surgical treatment was performed and tests showed that complete tumor necrosis was achieved in 66% of cases. The ablation rate correlated with the amount of energy given to tissue (2500J) or if temperature was raised to 60 deg. Celsius.

The Rush-Presbyterian-St. Luke's Medical Center published results from 54 cases with small breast carcinomas. Efficiency, safety and feasibility were tested in two time periods: 1994-2001 and 2000-2002 (40).

In 70% of treated cases complete ablation of tumor was achieved, and in the second series this efficiency was raised to 96% after some technical problems were solved. Some coagulated tumors formed cysts.

A number of protocols advocate surgical excision after ILTA (39, 41, 42). Inadequate tumor necrosis rate (66%) and incapability of treating larger tumors with one probe (39) are mentioned as drawbacks of ILTA. As in other hypertermic methods, MRI is useful in monitoring treatment (42).

Cryoablation (CA)

Although freezing was used back in 1850, it took until 1963 to implement it as treatment of liver tumors or resectable secondary lesions in liver (2). Gradually, this method is introduced in ophthalmology, dermatology and urology, and finally breast tumors (stage III and IV) (44, 45).

The tissue is frozen to as extreme temperature as possible, thereby causing necrosis, and alternating freezing and thawing enhances the effect. (46). A three step procedure is commonly used today (freeze-thaw-freeze), and tissue temperature is lowered to -180 deg. Celsius. Destruction of cells inside the frozen sphere is irreversible (Kaufmann CS, 2006) (47).

Freezing is usually achieved by means of liquid argon or nitrogen. Alternating cycles enhance damage inflicted on cells, and speed of cooling can further enhance the level of cell destruction (48).

An overview of the published protocols reveals the long duration of the procedure (52 minutes), followed by excision of the lesion after 1-5 days (30, 49). Only tumors smaller than 15 mm were completely necrotic. Efficiency is measured by level of cell membrane destruction. A test carried out on rats proved that one freeze-thaw cycle is not sufficient. After application of one cycle, 80% of tumors were still present, and after 5 cycles, the level of recurrence was down to 5% (48, 50).

Despite good results in animals (51, 52), cryoablation has not been introduced as therapy of breast cancer in humans. Many shortcomings were revealed during studies, with significant number of viable tumors after procedure and problematic assessment of size of ice ball on ultrasound (53).

CA showed that malignant tumor cells are far more resistant to cooling than to heating. Finally, the chemical ablation method by direct applica-

Table 2.

COMPARISON OF ABLATION METHODS FOR BREAST CANCER

Ablation type	**Duration**	**Energy transfer type**	**Equipment price**	**Success rate**	**Equip-ment**	**Training necessary**	**Out-patient or hospita-lised**	**Discomfort level**	**Anesthesia type**
RFA	10´-30´	Percutaneous	Low	92%	Minimal	Minimal	Both	Moderate	General or i.v. local
HIFU	30´-130´	Transcutaneous	High	?	Significant	Significant	Hosp.	Moderate	I.V.
MWA	20´-60´	Percutaneous	High	8%-60%	Medium	Medium	Hosp.	Moderate	I.V.
ILTA	25´-30´	Percutaneous	High	70%-96%	Significant	Significant	Hosp.	Moderate	General I.V. Local
KA	15´-30´	Percutaneous	Low	92%	Minimal	Minimal	Out-patient	Minimal	Local
Percutaneous Biopsy (excision)	10´-40´	Percutaneous	Low	40%-78%	Minimal	Minimal	Out-patient	Minimal	Local

Modified from: Cary S. Kaufmann. Breast cancer ablation: Current status 2006. Semin Breast Dis 2006; 9: 3-12

tion of ethanol during 10-15 minutes, although simple, did not have wider adoption and there are no significant publications (47).

CONCLUSION

All minimally invasive methods for local treatment of breast cancer have advantages of being simple to apply, causing less physical and psychological stress and cost less. All of them have to be proven in clinical trials, where efficiency needs to be comparable to BCS, as standard for treatment of early stage breast cancer (54).

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