Review Article

Cryosurgery in the treatment of women with breast cancer—a review

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Abstract: Cryoablation could be an alternative to surgical excision of breast cancer. The cytotoxic potential of cryosurgery has been shown in both animal models and studies conducted on humans. There are several advantages to be gained from ablation performed at very low temperatures and these include the method's simplicity, lack of pain, low morbidity, cost-effectiveness, and potential for positive cryo-immunologic effects. This manuscript reviews data concerning the use of cryoablation in the treatment of breast cancer.

Keywords: Cryoablation; cryosurgery; breast surgery; breast cancer

Submitted Feb 10, 2014. Accepted for publication Mar 20, 2014.
doi: 10.3978/j.issn.2227-684X.2014.03.04
View this article at: http://www.glandsurgery.org/article/view/3784/4710

Breast cancer is the most common malignancy and leading cause of cancer-related mortality in women. Although the problem still remains serious, some positive changes in the situation have been observed: due to dynamic development of imaging and population based screening programs there is now reduced mortality and the median diameter of tumors has decreased from 2 cm in 1990 to 1 cm (1). Another reduction concerns a decrease in the aggressiveness of the local treatment: most patients are suitable candidates for breast conserving therapy (BCT) instead of mastectomy. Amputation of the gland, when necessary, can be combined with immediate or delayed reconstruction. Sentinel node biopsy has replaced elective axillary lymph node dissection in cases without their clinical involvement. Although BCT allows mutilation to be avoided, the rate of negative cosmetic results after lumpectomy performed by means of "wide excision" is as high as 30% (2,3). In contrast, oncoplastic surgery of the breast gives favorable aesthetic outcomes, especially when combined with symmetrisation of the contralateral gland if needed; however, there are some patients who are unsuitable for this kind of treatment due to general contra-indications (i.e., cardiac or pulmonary insufficience) or lack of consent for surgery. Other, less aggressive options of locoregional treatment could be favorable, especially in this group of patients. Several methods have been proposed in this context with different energy sources: radio-frequency ablation (RFA) (4), laser-induced thermotherapy (LTT) (5), microwave ablation (MWA) (6), high-intensity focused ultrasound (HIFU) ablation (7) and cryodestruction. Being minimally invasive, they show some advantages compared to surgery: minimal incision, no scars, less pain, shorter recovery periods and thus higher cost-effectiveness (8). Advantages such as the possibility to perform ablation under local anaesthesia and the lack of pain are especially noticeable in the case of cryosurgery (9). According to the American College of Surgeons, any new emerging treatment modality should fulfill three criteria: it should be tested for safety and efficacy, its effectiveness should be the same as that described for any pre-existing therapeutic options, preferably with lower morbidity, and it should be cost-effective (10). Cryotherapy of breast tumors can be a feasible method for the eradication of malignant breast tumors. It has proven value in the destruction of cancer cells within the cryozone in different malignancies (skin cancers, liver and prostate tumors). The procedure can be performed in an outpatient clinic under local anaesthesia, without the need for an operating theater and the team usually involved in surgical interventions performed under general anaesthesia. Thus, the method is a cost-effective one. Furthermore, there should be no cave within breast parenchyma which usually follows the wide excision of a tumor, which causes breast asymmetry and poor cosmetic results. There is even another advantage of cryosurgery and this concerns its potential to enhance immunological response following cryoablation (11).

The achievent of improved results via the application of low temperatures in the treatment of women with breast cancer were described for the first time in 1850 by Arnott, who used iced saline solutions on women with locally advanced breast tumors (12). The technical development of adiabatic expansion systems introduced new cryogens such as liquid air, nitrogen and oxygen. Cryodestruction appeared to be a successful method for the treatment of patients with skin cancers. Construction of trocar cryoprobes in the second half of the 20th century allowed cryodestruction of tumors localised deep in parenchymal organs, i.e., liver, prostate and lung.

Eradication of breast tumors through cryoablations seems to be feasible due to the superficial localisation of the glands and thus their accessibility for both cryo-probes and imaging devices, i.e., ultrasound (US), and the absence of intervening vital organs within which could be damaged during the procedure leading to serious complications (9). Vessels larger than 5 mm in diameter avoid damage during cryoablation thanks to their own blood flow (13).

According to Kaufman, cryodestruction of breast cancer should be reserved for patients with small, unifocal tumors. Criteria for cryoablation exclude invasive lobular cancer as a histologic type, an extensive ductal carcinoma in situ (DCIS) component and a tumor diameter larger than 15 mm (1). Sabel *et al.* describe more than 25% of DCIS in core biopsies as contra-indication (14). According to Littrup *et al.*, who performed cryoablation of tumors in clinical stages I-IV with a multi-probe freeze approach, isotherms within cryozones can be accurately controlled and such cryoablation enables the destruction of much bigger lesions, up to 7 cm in diameter (15). Minimum imaging requires US, mammography and magnetic resonance of the breast (MRI). Hence, MRI does not show 31% of the low-grade *in situ* disease (16) and multiple core biopsies of surrounding tissues are advised to exclude an extensive intraductal component which could lead to a lack of radicality of cryoablation (1,9). Roubidoux proposed assessment of the disease using MRI and emphasized the importance of the quality of the biopsy, noting the possibility of an underestimation of a cancer's extension in poor quality specimens (17). Despite the significant cryodestructive potential of the multi-probe freeze approach, we must remember that cryodestruction is not a substitute for mastectomy. In a report on a multi-institutional trial studying cryoablation of early-stage breast cancer, Sabel *et al.* maintain that "every attempt should be made to exclude patients who may have a significant intraductal component" (14).

The procedure can be performed either with a single cryoprobe (13) or with more, at least two cryoprobes placed percutaneously under local anaesthesia directly into the lesion under US or MRI guidance. Multiprobe placement enables acquisition of isotherms lethal for cancer cells in larger volumes of tissue (15). Low temperature provides an additional anaesthetic effect, making the procedure even more tolerable for patients. An ice-ball formatted around the cryoprobe encompasses the entire tumor and surrounding breast tissue with an appropriate margin. Although after surgical excision sufficient and safe margins around the specimen should be free from cancer cells, making resection radical, those obtained during cryoablation should be 10 mm wide, as seen in real time ultrasound guidance. A total of 1 cm of visible ice covering all tumor margins allows the generation of a low, cytotoxic temperature to encompass all parts of the cryodestructed lesion. In cases of its localisation close to the skin, even 1-2 mm from the surface, saline injections enable acquisition of the required 1 cm margin and protect skin from necrosis. Warmed bags of saline and vigorous rubbing also prevent ice from penetrating the skin and possible complications (15,18). Roubidoux *et al.* described good results from the cryoablation of nine malignant breast lesions with ice-balls covering the tumor plus an 8-10 mm margin (17). A study performed on an animal model by Rabin *et al.* (19) showed an even narrower, 5 mm margin to be sufficient in the ablation of a sheep breast tumor. Cryosurgery is a clearly visualised technique due to the ice-ball formation seen in imaging. Tumor cells are destroyed through several mechanisms active during the freeze-thaw cycle. There are usually two such cycles performed in every case, each of them encompassing freezing followed by thawing, the second phase either active or passive. The longer the thawing phase is, the better the effect obtained (20). Intracellular ice formation present directly in the close vicinity of the cryoprobe causes membrane damage and cell death (21,22). In cells localised further from the probe the freezing phase encompasses extracellular rather than intracellular fluid which is protected by the lipid membrane; the high osmosis of the unfrozen part of the extracellular space causes osmotic imbalance and fluid shifting from the intracellular space and thus dehydration and further membrane damage. In the thawing part of the cycle, the intracellular compartment becomes hypertonic and attracts fluid, which enters the cell through the damaged membrane. Furthermore, freezing destroys microvasculature; platelet aggregation and vascular stasis following thawing lead to ischaemia and necrosis of the cancer cells (20).

However, there are only a few reports concerning the efficacy of malignant breast tumor cryoablation in humans; surgical excision with margins free of cancer cells combined with radiotherapy or mastectomy are the golden standard of locoregional treatment, while systemic therapy is administered depending on the analysis of prognostic factors and comorbidities. Most studies have investigated the effectiveness of very low temperatures in pathological examinations of excised breast tumors after previous cryodestruction. Rand et al described excision of a previously cryoablated tumor. An invasive ductal cancer of a diameter larger than 1.5 cm (1 cm × 2 cm) had been cryodestructed, then excised and examined under a microscope; the authors found no viable cancer cells within the specimen. "Cryolumpectomy" should be effective not only through destruction of tumor cells; rather, excision of the frozen tumor encompassed by an ice-ball could prevent spillage of cancer cells within the tumor bed (23). Litvinenko showed the benefit of cryodestruction performed under US guidance, preceding lumpectomy performed under US guidance. The frequency of local recurrences in the cryoablated group (80 patients) was much lower than in the group of patients who underwent lumpectomy without cryosurgery (76 patients): 1.3% *vs.* 9.2%. The 3-year overall survival in the first group was 85.7% compared to 65.0% in the second, control group (24). Tafra *et al.* described a similar situation after they had excised frozen breast tumors. Furthermore, they showed cryo-assisted localisation (CAL) to be an interesting and effective alternative to hook-wire localisation of non-palpable breast cancers. Excision of palpable ice-ball encompassing tumors is much easier for the surgeon than resection with use of the hook wire, often displaced during manoeuvres in the fatty tissue of the breast. Furthermore, in this study margins were free from cancer cells, while the volume of the resected breast parenchyma was lower compared to the traditional method (25). In another study, Tafra *et al.* compared CAL with needle-wire localisation in 310 patients: positive margin status was similar in both groups (28% *vs.* 31%), while the volume of the specimens was significantly lower in the CAL group (49 *vs.* 66 mL). CAL was easier to perform, the quality of the specimen was better, short term cosmesis and patient satisfaction were better in the first group. Although invasive cancer positive margin rates were lower in the CAL group (11% *vs.* 20%), there were higher ductal *in situ* positive margin rates (30% *vs.* 18%) (26).

Pfleiderer *et al.* performed cryodestruction of 16 breast cancers with the use of one cryoprobe for each lesion and observed no major side effects. Mean tumor diameter was 21±7.8 mm, and the diameter of the cryoprobe was 3 mm. The authors used one cryoprobe for each tumor, placed under US guidance. There were two freeze/thaw cycles; the median diameter of the ice ball was 28±2.7 mm. The lesions were further excised within 5 days following cryoablation. Histologic evaluation of the specimen showed complete necrosis of 5 tumors of diameter <15 mm, while the examination of the other 11 larger tumors showed viable cancer cells (13). In another study, Pfleiderer *et al.* reported total necrosis of 30 cryodestructed tumors of a maximum of 15 mm diameter, but residual cancer was observed in five patients with DCIS presence within cryozones; thus, cryoablation does not seem to be a suitable method for use in preinvasive disease of the breast. Rand *et al.* treated one patient with ductal cancer of a diameter larger than 1.5 cm (1 cm × 2 cm), which was cryoablated, then excised and examined under a microscope. No viable cancer cells were found in the specimen (23).

Sabel reported the effectiveness of cryoablation of 100% of tumors which were not larger than 10 mm and those of a diameter less than 15 mm but without *in situ* components. Cryoablation was not effective in tumors larger than 15 mm. The procedure was performed with the use of a single cryo-probe for each case (14). Roubidoux *et al.* performed cryosurgery of nine malignant tumors followed by excision 2-3 weeks after cryoablation. The mean size of the tumors was 12 mm (range: 8-18 mm). Seven of nine patients had no residual disease, while there was one small invasive focus in one case and extensive multifocal ductal *in situ* neoplasm in another one. These residual lesions were localised at the posterior margins of the cryodestructed tumors; their visibility is lower in US. The extensive intraductal component was occult in US (17).

Other studies have evaluated cryoablation of breast tumors performed under the guidance of MRI. This particular method of imaging enables visualisation of non-calcified DCIS. Morin *et al.* performed cryoablation followed by mastectomy on 25 patients with T2 tumors. Since there were only two lesions smaller than 2 cm, cryoablation of larger tumors gave bad results, as stated in the forementioned studies. Cryoablation was ineffective in 12 cases. It was possible to predict negative results based on the MRI imaging during the the procedure (27). Pusztaszeri *et al*. described cryodestruction of 11 tumors smaller than 20 mm. They reported skin necrosis in five cases (28). The negative predictive value of MRI in the post-ablation setting to determine residual in situ or invasive breast carcinoma has been evaluated in American College of Surgeons Oncology Group (ACoSOG) trial Z1072 titled "A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma" which is currently ongoing.

There are also studies describing the effect of cryoablation in cases when tumors have been left for follow-up without excision. A case report published by Staren described cryoablation of two separate but proximate synchronic tumors (0.8 and 0.5 cm in diameter; invasive lobular carcinoma in histology) present in the same breast and their total necrosis; the place of cryoablation was further assessed in pathologic examination of the specimen obtained through core biopsies. There were no viable cancer cells 12 weeks post procedure (29).

Littrup *et al.* described cryodestruction of 22 cancer foci in 11 patients in clincal stage I-IV, who refused surgery. Tumors were larger than those cryoablated in the forementioned studies: mean lesion diameter was 1.7±1.2 cm (range: 0.5-5.8 cm). There was also another difference concerning the number of cryo-applicators used for ablation. The authors performed multiprobe placement (with an average of 3.1 probes) under visualisation of cryoprobe position and ice-ball in US and computed tomography (CT). There were no significant complications following the procedure and, most importantly, there were no local cancer recurrences within breast MRI imaging follow-up lasting 18 months. Cryoablation was well-tolerated by patients: the average value of pain self-assessment was 0.4 on a 10-point scale, with the highest value 4 in two cases. Pain was well controlled with analgesics. There were no breast distortions after treatment (15).

There is concern about the lack of discrimination between scar present in the place of cryoablation and residual or recurrent tumors in follow-up and possible misinterpretation of imaging. However, the cryodestruced site was impossible to find 5 months after the procedure on a sheep model with use of imaging (US, mammography and MRI). Roubidoux *et al.* described changes found in US and mammography which corresponded to coagulative necrosis and fatty tissue necrosis following cryoablation (17). Wang *et al.* described the greatest reduction in ablation volume observed in the period between 3 and 24 months (30). Scars after cryoablation of benign breast lesions up to 2 cm in diameter were resorbed within 6 months, while those after cryosurgery of larger tumors disappeared within one year (31-33).

Based on our positive experience in cryodestruction of skin malignancies, supplementing reports about local treatment of patients with Paget's disease of the nipple (34) and our good results in treatment of patients with extramammary Paget's disease, we performed cryoablation of the nipple-areola complex (NAC) in a series of six cases of women with this rare form of breast malignancy. There were either general contra-indications for surgery by means of mastectomy (the kind of intervention proposed routinely at the time when the study was performed) or lack of consent for operations or both. We obtained very good results in terms of survival: there were two cases of recurrent disease treated successfully with repeat cryotherapy (35).

Cryotherapy has been described in the treatment of patients with locally advanced and/or disseminated breast carcinoma. The application of very low temperatures, either with a cryo-probe or spray provides benefit by inhibiting bulky tumor growth and decreasing odor. As shown in the studies presented below, cryodestruction is much more than the last method of palliative treatment performed for psychological reasons. The positive effect of cryoablation on inoperable cancers was described by Tanaka in four out of nine patients. He reported not only relief of pain and bulk reduction, but also prolonged survival (36).

There is some evidence that presentation of residual tumor protein following cryoablation can give additional benefit to a patient through enhancing her immunological response. Such a response could inhibit cancer metastases. Clinical observations of patients with remission of disseminated melanoma of the skin following cryosurgery support this hypothesis (37). Neel reported tumor-specific immunity in an animal model to be consistently higher after cryoablation than when measured after surgical excision (38). It seems that both stimulation and suppression can be triggered as a response to cryoablation. According to Sabel, the effect depends not only on the tumor type, but also on the technique: method of freezing (the length of time the lowest temperature is maintained, number of freeze/thaw cycles and the rates of the particular phases), volume of cancer frozen and the time of assessment (20). This shows cryosurgery to be especially attractive for patients with dissemination to skin, chest wall recurrences and/or bulky tumors (39).

Cryodestruction of malignant breast tumors can be an attractive alternative to surgery for patients not suitable for the standard form of treatment due to general contra-indications and/or a lack of consent for surgery. Proper staging allows cases with extensive intraductal components to be identified and excluded. The procedure is cost-effective and can be performed in an outpatient clinic. The lack of need for general anaesthesia and the short recovery period could be highly attractive, especially for women with comorbidities which might increase the risk of perioperative complications. Method seems to be effective and safe tool of treatment of patients with breast cancer in the evidence of the aforementioned studies. However, the existing evidence is inadequate to recommend cryosurgery of breast cancers as alternative to surgical excision, which remains golden standard. The potential of this treatment to act as a replacement for lumpectomy depends on the results of the ongoing Z1072 trial and also future studies (22).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Tarkowski R, Rząca M. Cryosurgery in the treatment of women with breast cancer—a review. Gland Surgery 2014;3(2):88-93. doi: 10.3978/j.issn.2227-684X.2014.03.04

