



Cryosurgery for primary breast cancers, its biological impact, and clinical outcomes

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Abstract

Recently, a number of new minimally invasive image-guided percutaneous ablation treatments, including cryoablation, radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, laser ablation, and irreversible electroporation have been developed. Several studies have shown the feasibility and safety of these cryoablation therapies for the treatment of benign breast tumors and small invasive breast cancer. Although the complete response rate of cryoablation for breast cancer is reported to be relatively good, most studies enrolled a small number of patients, and so reliable conclusions could not be drawn. In this review, we introduce the mechanisms of action of cryoablation, and summarize the current literature on the efficacy and safety of cryoablation for breast cancer. Cryoablation also induces an immunomodulatory effect, which is an interesting topic of research in the era of immune checkpoint inhibitors. Cryoablation for primary tumor may enhance the treatment effect of immune checkpoint inhibitors in patients with breast cancer. Further investigations of this new therapeutic strategy are needed.

Keywords Breast neoplasm · Ablation techniques · Cryosurgery · Immunotherapy

Introduction

Breast cancer is the most common tumor among women worldwide, with about 1.7 million cases diagnosed in 2012 [1]. The trend in surgical treatment for breast cancer has been toward less-invasive techniques. Although total mastectomy is still performed in some patients, breast-conserving surgery followed by radiation therapy has been established as an oncologically safe approach for patients with early breast cancer [2]. Multidisciplinary treatment including systemic therapy has also contributed to the trend toward minimally invasive local treatment.

Recently, a number of new minimally invasive image-guided percutaneous ablation treatments have been developed. The techniques include cryoablation, radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, laser ablation, and irreversible electroporation. Several studies have shown the feasibility of these ablation therapies in the treatment of benign breast tumors, metastatic

hepatic tumors, and small invasive breast cancer [3]. However, most studies enrolled a small number of patients, and so reliable conclusions could not be drawn.

Cryoablation has a relatively long history compared with the other ablation techniques and was first used to treat breast and uterine cancers in the 1840s. In the 1960s, modern percutaneous cryoablation became feasible with technical advances such as delivery of liquid nitrogen through trocar-type probes. Since then, the technique has been used for various types of cancers, including skin, prostate, kidney, liver, lung, bone, and breast cancers.

In this review, we introduce the mechanisms of action of cryoablation, and summarize the current literature on the efficacy of cryoablation for breast cancer. We also discuss its synergy with immunotherapy.

Mechanisms of cryogenic cell death

Cryoablation causes freezing by circulating liquid nitrogen or rapidly decompressing argon gas at the distal end of a cryoprobe, thereby creating an ice crystal ball. Cryoablation induces cell injury through alternating freezing and thawing cycles. Four biological mechanisms of cryoablative injury have been described: direct cellular

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injury, vascular injury and ischemia, apoptosis, and immunomodulation [4].

In the freezing phase, the water in the extracellular space freezes before the intracellular water. The subsequently increased extracellular osmotic pressure induces intracellular dehydration resulting in cell shrinkage and distortion of the plasma membrane, which is enhanced by ice crystal formation within the cells. In the thawing phase, the intracellular space becomes hypertonic and the consequent inflow of liquid leads to cell rupture.

Cryoablation causes endothelial damage in the microvasculature. This leads to platelet aggregation, microthrombosis, and ischemia. Vasoconstriction also occurs in response to the fall in temperature, resulting in ischemic tissue death followed by coagulative necrosis.

Coagulative necrosis occurs in the central zone of the cryoablative lesion as a result of direct cold injury and vascular injury. In addition, it has been shown that sublethal cryo-injury in the tumor peripheral zone can induce apoptosis in some cells [5].

The observation that metastatic tumors sometimes regress after cryoablation of the primary tumor, called the “abscopal effect”, has been reported in case reports and case series [6, 7]. Kumar et al. reported a rare case of a cryoablation-induced abscopal effect on axillary metastases [8]. The immunomodulatory effect of cryoablation will be discussed later.

Procedures

Eligibility criteria for cryoablation include unifocal tumor, tumor size less than 2 cm, location at least 1 cm from the skin surface, and lack of an in situ component (usually < 25% intraductal component) [9, 10]. There was a consensus agreement at Kyoto Breast Cancer Consensus Conference 2016 that luminal A-like, tumor size less than 1.5 cm, clinically node negative, and localized lesion on imaging study are eligible criteria for cryoablation (data not shown). One or more probes are inserted percutaneously into the center of the lesion, typically under ultrasound guidance. It is recommended that ice ball formation should cover an area 1 cm larger than the extent of the tumor to ensure complete ablation. The extent of delineation of the ice ball can be recognized on ultrasound, computed tomography, and magnetic resonance imaging (MRI). Subcutaneous injection of saline is sometimes required as a form of skin protection. Notably, the pectoralis muscle is generally unaffected by cryoablation. Local anesthesia is usually sufficient for the procedure in this site. Two freeze-and-thaw cycles with various durations are most often used.

Current evidence

Table 1 summarizes results from clinical trials of cryoablation for breast cancer. The complete response rate of cryoablation ranged from 36 to 100%. Most procedures were conducted under local anesthesia using ultrasound guidance. In 8 studies, surgery was performed after cryoablation, but in 6 studies, surgery was not performed. In a multi-institutional prospective study by Sabel et al. 29 patients with early breast cancer were treated with cryoablation [9]. In this trial, all the patients underwent surgical resection after cryoablation, which was successfully performed in 27 (93%) of 29 patients; pathological evaluation showed no residual viable invasive cancer in 23 (85%) of 27 patients. There were no complications from the procedures. The authors suggested that size of the tumor and the presence of an intraductal component affect the degree of residual tumor after cryoablation.

Mauri et al. reported a systematic review and meta-analysis of earlier studies on image-guided percutaneous ablation procedures for breast cancer [11]. The pooled rate of technical success, defined as the rate of patients in whom the operator was able to technically complete the ablation procedure, was 95% (range 90–98%), and the pooled rate of technical efficacy, defined as the rate of lesions completely ablated, was 75% (51–90%) for cryoablation.

The American College of Surgeons Oncology Group (ACOSOG) Z1072 is a phase 2 trial exploring the effectiveness of cryoablation in the treatment of breast cancer [10]. Eligibility criteria for this trial included unifocal invasive ≤ 2 cm, with $\leq 25\%$ intraductal component and tumor enhancement on MRI. All patients underwent surgical resection of the primary tumor within 28 days after cryoablation. The primary endpoint was the rate of complete tumor ablation, defined as no remaining invasive breast cancer or ductal carcinoma in situ on pathologic examination of the targeted lesion. Final pathology results showed successful ablation in 66 (76%) of 87 lesions (90% CI 67–83%). When multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure, successful ablation was achieved in 80 (92%) of 87 lesions.

Machida et al. evaluated findings on serial MRI after cryoablation for breast cancer without subsequent surgical resection [12]. Eligibility criteria were ductal carcinoma in situ or invasive carcinoma ≤ 15 mm, nuclear grade 1 or 2, estrogen receptor positive/human epidermal growth factor 2 negative without lymph node metastasis. During a mean follow-up of 40.6 (range 25–104) months, 1 of 54 patients experienced ipsilateral breast cancer recurrence and underwent mastectomy. Suspicious residual lesion was reported in 7 patients at the first post-cryoablation MRI

Table 1 Summary of clinical studies of cryoablation

Author, year	No. of patients	No. of tumors	Type of study	Inclusion criteria	Age (median/mean, range)	Tumor size (median/mean, range) (mm)	Anesthesia	Imaging guidance	Technical success rate	Complete response rate	Minor complications	Major complications	Subsequent surgical resection	Follow-up imaging study after cryoablation
Sabel, 2004 [9]	29	29	Prospective	$T \leq 20$ mm	52.5, 34–77	12, 6–20	Local	US	93.1%	85.1%	0.0%	0.0%	Yes	No
Morin, 2004 [25]	25	25	Prospective	Candidate for mastectomy	60, 41–77	28, 12–60	Local	MRI	100.0%	52.0%	0.0%	0.0%	Yes	No
Pfeiderer, 2005 [26]	30	30	Prospective	$T \leq 20$ mm	61.5, 46–80	12, 5–15	Local	US	96.7%	82.7%	6.7%	0.0%	Yes	No
Pusztasz- eri, 2007 [27]	11	11	Prospective	$T < 20$ mm	63, 52–78	30, 12–60	Local	MRI	90.9%	36.4%	0.0%	45.5%	Yes	No
Littrup, 2009 [28]	21	22	Prospective	Any stage	NA	17, 5–58	Local	US, CT	100.0%	100.0%	0.0%	0.0%	No	MRI
Manenti, 2013 [29]	40	40	Retrospec- tive	$T \leq 20$ mm, unifocal, G1-2	73, 64–82	NA	Local	US	100.0%	95.0%	2.5%	0.0%	Yes	MRI
Puseddu, 2014 [30]	17	19	Retrospec- tive	Stage IV	59, 37–81	25, 10–67	Local	CT	100.0%	88.0%	82.0%	0.0%	No	CT, MRI
Gajda, 2014 [31]	53	53	Retrospec- tive	Any stage	61, 38–81	15.3, 5–37	Local	US	96.2%	54.7%	NA	NA	Yes	No
Cazzato, 2015 [32]	23	23	Prospective	$T \leq 30$ mm, unifocal, post-menopausal, decline or unfit for surgery	85, 56–96	14, 5–28	Local	US, CT	100.0%	78.2%	21.7%	4.3%	No	MRI
Poplack, 2015 [33]	20	20	Prospective	$T \leq 15$ mm	NA	0.9–1.5	Local	US	100.0%	85.0%	50.0%	0.0%	Yes	No

Table 1 (continued)

Author, year	No. of patients	No. of tumors	Type of study	Inclusion criteria	Age (median/mean, range) (mm)	Tumor size (median/mean, range) (mm)	Anesthesia	Imaging guidance	Technical success rate	Complete response rate	Minor complications	Major complications	Subsequent surgical resection	Follow-up imaging study after cryoablation
Simmonds, 2016 [10]	86	87	Prospective	$T \leq 20$ mm, unifocal	62, 42–81	1.2, 0.5–1.9	Local	US	100.0%	75.9% (92% NA if multifocal tumor was excluded)	NA	NA	Yes	No
Pusceddu, 2017 [13]	35	35	Prospective	Stage IV	58, 37–81	30, 13–67	Local	CT	100.0%	85.7%	82.0%	0.0%	No	MRI
Machida, 2018 [12]	54	54	Prospective	$T \leq 15$ mm, G1-2, luminal	54.8, 37–72	8.5, 3–14	Local	US	100.0%	98.1%	NA	NA	No	MRI
Beji, 2018 [14]	17	17	Retrospective	Stage IV	54.8, 37–72	16, 5–45	Local	US, CT	100.0%	88.2%	5.9%	0.0%	No	MRI

acquired 20–60 days after cryoablation. However, at the second post-cryoablation MRI performed 126–348 days after cryoablation, all of the 7 patients were diagnosed as negative for residual disease.

Cryoablation for primary tumor in patients with Stage 4 breast cancer was also investigated. Pusceddu et al. reported that complete tumor necrosis was observed at 2 months after cryoablation in 30 (85.7%) of 35 patients with Stage 4 disease [13]. Beji et al. showed that 15 (88.2%) of 17 patients with Stage 4 disease achieved complete regression of the primary breast lesion without recurrence [14]. Five patients who initially had pain due to the primary lesion received immediate and complete relief after cryoablation.

Immunologic response to cryoablation

Cryoablation can induce both increased and reduced anti-tumor immunity. Coagulative necrosis of the tumor cells in the central zone of the lesion induced by cryoablation may optimize the presentation of tumor-specific antigens to the immune system, which results in T-cell activation and proliferation. In a mouse model, cryoablation resulted in tumor-specific T-cell response in regional lymph node, and increased NK cell activity [15]. In contrast, some tumor cells undergo apoptosis in the peripheral zone of the tumor lesion. When antigen-presenting cells, such as dendritic cells and macrophages, phagocytose tumor cells after apoptosis without danger signals, tumor antigens are presented on MHC class 1 molecules without co-stimulation of T cells. The dying cells can even secrete immunosuppressive cytokines, such as interleukin-10 and transforming growth factor- β . This induces anergy and clonal deletion [4]. It is, thus, difficult to predict whether the immunostimulatory effect or the immunosuppressive effect exerts more influence, and therefore, the abscopal effect induced by cryoablation is a rare phenomenon [8].

The immunomodulatory effect induced by cryoablation has led to exploration of cryoablation in combination with systemic immunotherapy. Liang et al. investigated the clinical benefits of cryoablation in combination with NK cell therapy and trastuzumab for HER2-positive recurrent breast cancer [16]. The three-combination therapy showed an improved response rate of the tumor, reduced levels of circulating tumor cells and tumor markers, and prolonged progression-free survival compared with cryoablation alone.

In a pilot study conducted at Memorial Sloan Kettering Cancer Center, 19 breast cancer patients were treated with preoperative tumor cryoablation ($n = 7$), a single dose of the anti-CTLA-4 antibody ipilimumab ($n = 6$), or both ($n = 6$) [17]. The primary endpoints were safety and tolerability. Preoperative cryoablation plus ipilimumab was safe and tolerable, with no delays in pre-planned surgery

and only 1 case of a grade-3 adverse event (unrelated rash after ipilimumab). Exploratory analyses showed that combination therapy was associated with sustained peripheral elevation in Th1-type cytokines, activated and proliferating CD4+ and CD8+T cells, and post-treatment proliferative T-effector cells relative to T-regulatory cells within the tumor. They also showed that compared with monotherapy, the combination of cryoablation and ipilimumab was associated with robust expansion of numerically greater numbers of peripheral blood and intratumoral T-cell clones following therapy [18].

Immunotherapy trials of immune checkpoint inhibitor monotherapy have focused on patients with metastatic triple-negative breast cancer. However, observed response rates to immunotherapy in breast cancer are modest compared with other tumors, such as melanoma and non-small cell lung cancer [19–23]. Combining chemotherapy or radiotherapy may enhance response by increasing immunogenicity or overcoming immune escape mechanisms. The IMpassion130 trial, a phase-3 trial of atezolizumab in combination with nab-paclitaxel compared with placebo and nab-paclitaxel in treatment-naïve metastatic triple-negative breast cancer, showed a relatively good response rate of 56% [24]. Combining cryoablation with immunotherapy also has the potential to increase immunogenicity, and thus further investigations are needed.

Conclusion

Retrospective and prospective studies have shown the feasibility and safety of cryoablation for early breast cancer treatment. The phase 2 ACOSOG Z1072 trial showed a relatively good complete response rate following cryoablation. Two other phase-2 trials, the FROST trial (NCT01992250) and the Ice3 trial (NCT02200705), are currently under way to evaluate complete response or local recurrence after cryoablation without subsequent surgery in breast cancer patients with maximum tumor size ≤ 1.5 cm. The immunomodulatory effect induced by cryoablation is an interesting topic of research in the era of the immune checkpoint inhibitors. Cryoablation for primary tumor may enhance the treatment effect of immune checkpoint inhibitors in patients with breast cancer. Further investigations of this new therapeutic strategy are needed.

Compliance with ethical standards

Conflict of interest M. Takada has received honoraria from Chugai, AstraZeneca, Kyowa Hakko Kirin, and Eisai; and has received a research Grant from Eisai. M. Toi has no conflict of interest to disclose.

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