

Advances in the application of cryotherapy to the treatment of breast cancer

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Abstract

Cryotherapy is a minimally invasive treatment. With increasing rate of breast cancer detection, ablation therapy has become an alternative approach for the treatment of this pathology due to its advantages of minimally invasive, fewer complications, good efficacy, and repeatability. Preclinical and clinical studies of cryotherapy for breast cancer published through December 2022 were identified through a literature search using PubMed, ClinicalTrials.gov, and CNKI. This article reviews the progress of cryoablation in the treatment of breast cancer.

Keywords

breast cancer; cryoablation

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1 Mechanism and principle of cryotherapy

Cryotherapy is an ablation technique that uses freezing instead of thermal effect to destroy tumor cells, leading to tumor tissue necrosis^[1-3]. Periodic freezing and thawing of preset target areas can physically destroy tumor tissue structure by using argon-helium knife or Combo knife freezing equipment with automatic probe, which has been successfully applied to the clinical treatment of solid tumors such as skin tumors, advanced liver cancer, breast cancer, colorectal cancer liver metastases and bladder cancer^[4-7].

As a minimally invasive local physiotherapy, cryotherapy has the following significant advantages compared with surgical resection, systemic chemotherapy, and targeted therapy. (1) Unlike surgical resection of tumors, cryotherapy creates a smaller wound and therefore can reduce the incidence of surgical incision infection and/or other complications^[8]. (2) Under the guidance of B-ultrasound, CT or MRI, cryotherapy can achieve real-time monitoring and accurate temperature measurement and avoid damage to normal tissues around cancer to the greatest extent^[9]. (3) Cryotherapy has less stringent requirements for anesthesia in clinical operation, which increases the acceptance degree of patients to a certain extent^[10]. For patients with postoperative tumor recurrence, whose body cannot tolerate surgery or radiotherapy or chemotherapy or whose tumor location is special and cannot be operated, application of cryotherapy can rapidly reduce the

tumor load, improve the quality of life, and lay a foundation for the application of other treatments, due to its simple operation and repeatable applications. It is worth noting that for surgical applications, the efficacy of cryotherapy largely depends on the operation level, and the local reaction following cryotherapy could be more severely manifested with local edema, ooze, secondary infection, and even nerve involvement, as well as other adverse effects^[11].

With increasing clinical applications of cryotherapy, research on its therapeutic mechanisms is continuously deepening. Currently, it is believed that the efficacy of cryotherapy in the treatment of solid tumors could be ascribed to the following mechanisms. (1) In the initial stage of cryotherapy, ultra-low temperature argon can rapidly reduce the temperature of tumor tissue in the target area down to about -160°C, and a large number of ice crystals formed inside and outside tumor cells to puncture tumor cell membranes, thus causing dehydration and death of tumor cells^[12]. (2) Following tumor cell necrosis, microthrombus can be formed in local tissues to block the blood supply of tumor tissues thereby restricting the growth of tumor^[13]. (3) Tumor cells express large amounts of tumor-associated antigens (TAA), which are difficult to be recognized by the immune system in the immune microenvironment of tumor patients. Cryotherapy can lyse tumor cells, and the antigen-presenting cells (APC) represented by macrophages and dendritic cells can recruit the TAA into cytotoxic T lymphocytes (CTL) and B lymphocytes after engulfing the

Table 1 Comparison of application of cryotherapy in patients with different pathological types of breast cancer

Researcher	Pathological classification of breast cancer	Sample size	Research type	Intervention measures	Results
Morin <i>et al.</i> ^[20]	Invasive breast cancer	25	Randomized controlled clinical trials	MRI guided argon-helium cryoablation	13 cases of complete ablation, 2 cases of partial ablation, 10 cases of failure
Littrup <i>et al.</i> ^[21]	Invasive breast cancer	11	Randomized controlled clinical trials	CT-guided argon-helium cryoablation	11 cases of complete ablation
Ward <i>et al.</i> ^[22]	Invasive breast cancer	23	Retrospective study	B-ultrasound-guided argon-helium cryoablation	14 cases of complete ablation, 7 cases of partial ablation, 2 cases of failure
Pusztaszeri <i>et al.</i> ^[23]	Intraductal breast cancer	11	Randomized controlled clinical trials	Argon-helium cryoablation	2 cases of complete ablation, 9 cases of partial ablation

ruptured tumor cells rendered by cryotherapy. In this way, cryotherapy produces synergistic anti-tumor effects through humoral and cellular immunity. Such a mechanism helps remove tumor cells, especially tumor stem cells that are resistant to chemotherapy, and prevent the recurrence of seed tumor^[14]. In addition to eliminating non-necrotic tumor cells, activated cytotoxic T lymphocytes by cryotherapy can also migrate to other tumor tissues and elicit their immune killing effects^[15]. Activated B lymphocytes can also play the role of immune clearance and immune regulation by secreting specific antibodies^[16]. (4) The pathological examination of tumor tissues following cryotherapy showed that the central part of the cryotherapy-targeted area was transparent necrosis, whereas normal living cells were present intact around the targeted area. Therefore, the target area of cryotherapy should be set slightly larger than the tumor tissue boundary to avoid residual tumor tissue^[17]. Studies published to date have found that mutation of tumor suppressor gene TP53 and the regulation of genes at the level of single nucleotide polymorphism (SNP), plays an important role in the development of breast cancer, while acquired factors such as lifestyle, carcinogen exposure and intestinal flora are also involved in the progression of breast cancer to varying degrees^[6,15]. Therefore, given the fact that different types of breast cancer respond differently to different treatments, future studies should focus on the role of the corresponding biomarkers in recommending cryotherapy.

2 Current progress of cryotherapy

Breast cancer is a type of solid tumor with high incidence in women. With the improvement of early detection rate, the incidence of breast cancer has increased year by year in recent years^[16]. At present, surgical resection is the main treatment for breast cancer, but for patients with early breast cancer who have breast conserving desire and negative lymph metastasis or who are not suitable for radical resection of breast cancer, cryotherapy can replace surgical therapy for tumors in their early stages, which can reduce the tumor load in advanced patients and extend the survival period of patients^[18-19].

Based on the experience of cryotherapy in the treatment

of colorectal cancer with liver metastasis and breast benign tumors, some researchers studied the feasibility of cryoablation for invasive breast cancer (Table 1). Morin *et al.*^[20] performed cryoablation in 25 cases of invasive breast cancer with only 2 lesions less than 2 cm under the guidance of MRI, among which 13 cases had all lesion tissues completely ablated without serious complications, and histopathologic examination showed no residual cancer cells in the lesion tissues following ablation. Two patients were found to have incomplete treatment of cryotherapy lesions, and 10 have teardrop-like ice balls formed in the lesions during treatment, leading to treatment failure. This study suggests that MRI guided cryotherapy is feasible for invasive breast cancer; yet the operation manners and imaging results during the treatment have important impacts on the treatment outcome.

Littrup *et al.*^[21] performed argon-helium cryoablation in 11 patients with early breast cancer. All patients underwent CT-guided surgery within 45 minutes, and all tumors were completely ablated in 11 patients. Ward *et al.*^[22] performed cryoablation for invasive breast cancer guided by B-ultrasound, and 61% of patients' tumor tissues were completely ablated, showing the powerful anti-tumor efficacy of cryoablation. Pusztaszeri *et al.*^[23] performed cryoablation on 11 patients with intraductal breast cancer, but only 2 cases achieved complete remission, and the residual tumor tissue after cryoablation was higher than that of invasive breast cancer, suggesting that intraductal breast cancer was not sensitive to cryotherapy. Therefore, in the treatment of early breast cancer, diagnosing the pathological type of breast cancer should be achieved prior to selection of an appropriate treatment. Notably, local treatment using cryotherapy or radiotherapy in combination with immune checkpoint blockade has shown promising results in clinical trials on the treatment of triple negative breast cancer^[24].

In summary, cryotherapy, a local minimally invasive surgical technique, offers many advantages such as easy operation and significant therapeutic effect, and the prospect of cryotherapy application to breast cancer treatment deserves further study and promotion.

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Conflicts of interest

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